Full title: A phase 1 safety and immunogenicity study of a Crimean-Congo haemorrhagic fever virus vaccine, ChAdOx2 CCHF, in healthy adult volunteers in the UK

Short title: CCHF01: A study of a new vaccine against Crimean-Congo Haemorrhagic Fever (a life-threatening tick-borne viral disease)

Internal Reference Number: OVG2022/05

Protocol Version: 2.0

Date: 14th July 2023

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Lead Scientific Investigator: Professor Teresa Lambe

Sponsor: University of Oxford

Funder: UK Research and Innovation

REC Details: <<rec name/address>>

REC Number: <<#>>

EudraCT Number: 2022-003889-20

IRAS Reference: 1007128

ISRCTN Registry Number: <<#>>

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1 KEY TRIAL CONTACTS

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2 LAY SUMMARY

This is a study of a new vaccine against Crimean-Congo haemorrhagic fever (CCHF) virus in healthy adults.

CCHF is a potentially fatal viral illness spread by ticks, which can live on many wild and domestic animals, including cattle, sheep and goats. Humans usually acquire CCHF infection following a tick bite, although it can also be acquired from contact with blood or tissues from infected animals or humans. Infection may be asymptomatic, but it can cause severe disease with impaired blood clotting leading to serious bleeding and death. The disease occurs over a wide geographical area including southern Europe, Africa, south-east Asia and the Middle East. According to World Health Organisation estimates, 3 billion people are at risk from CCHF, and there are 10,000 to 15,000 cases each year, resulting in 500 deaths.

The study vaccine is called ChAdOx2 CCHF. It has been developed by the University of Oxford, using similar technology to the Oxford/AstraZeneca COVID-19 vaccine. This study will be the first to give this vaccine to humans. Its purpose is to assess the tolerability and safety of the vaccine and to measure immune responses after vaccination. The study will also investigate whether having received other similar (adenovirus based) vaccines in the past affects the response to ChAdOx2 CCHF.

We plan to recruit 46 people aged between 18 and 55 years. Volunteers will be screened for eligibility with an initial online questionnaire followed by an in-person medical assessment. Eligible participants will be invited to attend the first vaccination visit. A second vaccination will be given approximately 12 weeks later. Participants will record symptoms after each vaccination in an e-diary. Blood tests will be taken to assess response to the vaccinations. Adverse events will be recorded throughout the trial and participants will be followed up for 1 year.

3 SYNOPSIS

Trial Title	A phase I safety and immunogenicity study of a CCHF virus vaccine, ChAdOx2 CCHF, in healthy volunteers aged 18 to 55 in the UK
Trial Sites	**Site 1:** Oxford Vaccine Group Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) Churchill Hospital, Oxford **Site 2: University Hospital Southampton NHS Foundation Trust** Tremona Road Southampton SO16 6YD **Site 3 – non-recruiting: Oxford University Hospitals Foundation Trust** Headley Way, Headington, Oxford OX3 9DU
Funder	UK Research and Innovation
Trial Code	CCHF01
Study Design	First-in-human, multi-centre, open-label phase I clinical trial with an initial lead-in cohort (Cohort 1)
Vaccine Schedule	2 doses, given at 0 weeks and 12 weeks
Population	Healthy adults aged 18 to 55 years, with or without previous exposure to an adenoviral-vectored vaccine
Planned Sample Size	46 participants (6 in Cohort 1; 40 in Cohort 2)
Follow-up Duration	12 months (from the first vaccination)
Primary Objective	To assess the safety and tolerability of ChAdOx2 CCHF in healthy adult volunteers
Secondary Objective	To assess the immunogenicity of ChAdOx2 CCHF in healthy adult volunteers
Investigational Product	ChAdOx2 CCHF (5×10^{10} viral particles (vp) per dose administration)
Route	Intramuscularly (IM) into the deltoid region of the arm

Cohort	Group	Number of participants	Age (years)	Previous ChAdOx vaccine	Intervention 1 (D0)	Intervention 2 (D84)	Follow-up
1		6	18-55	Either Yes or No	$5x10^{10}$ vp	$5x10^{10}$ vp	1 year

					ChAdOx2 CCHF	ChAdOx2 CCHF	
2	A	20	18-55	Yes	$5x10^{10}$ vp ChAdOx2 CCHF	$5x10^{10}$ vp ChAdOx2 CCHF	1 year
	B	20	18-55	No	$5x10^{10}$ vp ChAdOx2 CCHF	$5x10^{10}$ vp ChAdOx2 CCHF	1 year

4 SCHEDULE OF PROCEDURES TABLES

4.1 Schedule of procedures table: Screening visit (all volunteers)

Table 1 Schedule of procedures: Screening Visit (all volunteers)

Visit Number	S
Visit type	Screening
Timeline[1]	7 to 90 days before D0
Visit Procedures	
Informed consent	X
Review inclusion and exclusion criteria	X
Record demographic data	X
Medical history[2]	X
Vital signs (heart rate, temperature, blood pressure)	X
Screening physical examination	X
TOPS registration *www.tops.org.uk*	X
Urine Samples	
High-sensitivity Urinary HCG (POCBP only)	X
Stool Samples (Optional)*	
Sample containers and instructions provided	(X)*
Blood Samples[3]	
HBsAg, HCV Ab, HIV serology (mL)	~5
Biochemistry, haematology (mL)	~5
Blood volume per visit (mL)	~10
Cumulative blood volume (mL)	~10

[1]Additional unscheduled screening visits may occur (for example: to repeat a blood test, for safety or where clinically indicated)

[2]Medical history may be initially assessed by a telephone call prior to screening (see section 9.2); information obtained in this way will be reviewed at the screening visit

[3]Minor differences in blood volumes may occur depending on the collection tubes and equipment used (~ = approximately); additional repeat blood draws may be required (for example, if there is a problem with the sample or result abnormality)

* For Cohort 2 participants only

() = optional

4.2 Schedule of procedures table: Vaccination and follow up visits (Cohort 1)

Table 2 Schedule of procedures: Vaccination and follow up visits (Cohort 1)

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Visit type	Vac1	f/u	f/u	f/u	f/u	f/u	Vac2	f/u	f/u	f/u	f/u	f/u	f/u	f/u
Timeline[1]	D0	D2	D7	D14	D28	D56	V2 D84	V2 +2	V2 +7	V2 +14	V2 +28	V2 +56	V2 +140	V2 +280
Time window (days)		±1	±3	±3	±3	±7	±14	±1	±3	±3	±3	±7	±28	±60
Visit Procedures														
Review contraindications, inclusion and exclusion criteria	X						X							
Vaccination	X						X							
Vital signs (heart rate, temperature, blood pressure)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Targeted medical history/physical examination, if required[4]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse Event Collection														
Solicited AE collection	D0 to D7						V2 to V2+7							
Unsolicited AE collection	D0 to D28						V2 to V2+28							
SAEs & AESI collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review ongoing AEs		X	X	X	X	X	X	X	X	X	X	X	X	X
Electronic diary (eDiary)[2]														
Electronic diary started	X						X							
Electronic diary review (in clinic)		X	X	X	X			X	X	X	X			
Electronic diary closed					X						X			
Urine Samples														
High-sensitivity Urinary hCG (POCBP only)	X						X							X

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14

Visit type	Vac1	f/u	f/u	f/u	f/u	f/u	Vac2	f/u	f/u	f/u	f/u	f/u	f/u	f/u
Timeline[1]	D0	D2	D7	D14	D28	D56	V2 D84	V2 +2	V2 +7	V2 +14	V2 +28	V2 +56	V2 +140	V2 +280
Time window (days)		±1	±3	±3	±3	±7	±14	±1	±3	±3	±3	±7	±28	±60
Blood Samples[3]														
HLA typing (mL)	~4													
Biochemistry, Haematology (mL) [LFTs U+Es, FBC]	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5
Immunology (mL)	~50			~50	~50	~50	~50			~50	~70	~50	~50	~50
Blood volume per visit (mL)	~59	~5	~5	~55	~55	~55	~55	~5	~5	~55	~75	~55	~55	~55
Cumulative blood volume (mL)	69	74	79	134	189	244	299	304	309	364	439	494	549	604

[1]Additional unscheduled visits may occur (for example: to repeat a blood test, for additional clinical review)

[2]eDiaries are remotely monitored in (near) real-time for the occurrence of grade ≥3 AEs and daily for non-completion

[3]Minor differences in blood volumes may occur depending on the collection tubes and equipment used (~ = approximately); additional repeat blood draws may be required (for example: if there is a problem with the sample, abnormality in the results, or participant unwell)

[4] optional, at the discretion of the investigator

4.3 Schedule of procedures table: Vaccination and follow up visits (Cohort 2)

Table 3 Schedule of procedures: Vaccination and follow up visits (Cohort 2)

Visit Number	1	2	3	4	5	6	7	8	9	10
Visit type	Vac1	f/u	f/u	f/u	Vac2	f/u	f/u	f/u	f/u	f/u
Timeline[1]	D0	D1	D14	D28	V2 (D84)	V2 +1	V2 +14	V2 +28	V2 +140	V2 +280
Time window (days)		±0	±3	±3	±14	±0	±3	±3	±28	±60
Visit Procedures										
Review contraindications, inclusion and exclusion criteria	X				X					
Vaccination	X				X					
Vital signs (heart rate, temperature, blood pressure)	X	X	X	X	X	X	X	X		
Targeted medical history/physical examination, if required	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse Event Collection										
Solicited AE collection	D0 to D7				V2 to V2+7					
Unsolicited AE collection	D0 to D28				V2 to V2+28					
SAEs & AESI collection	X	X	X	X	X	X	X	X	X	X
Review ongoing AEs		X	X	X	X	X	X	X	X	X
Electronic diary (eDiary)[2]										
Electronic diary started	X				X					
Electronic diary review (in clinic)		X	X	X		X	X	X		
Electronic diary closed				X				X		
Urine Samples										
High sensitivity Urinary hCG (POCBP only)	X				X					X
Stool samples [optional]										
Home collection of stool samples[5]	[X]		[X]				[X]			[X]
Blood Samples[3]										
HLA typing (mL)	~4									
Biochemistry, Haematology (mL) [LFTs, U+Es, FBC]	~5	~5	~5	~5	~5	~5	~5	~5	~5	~5
Immunology (mL)	~50	~30	~50	~50	~50	~30	~50	~70	~50	~50
PAXgene (ml)	~2.5	~2.5			~2.5	~2.5				
Blood volume per visit (mL)	~61.5	~37.5	~55	~55	~57.5	~37.5	~55	~75	~55	~55
Cumulative blood volume (mL)	71.5	109	164	219	276.5	314	369	444	499	554

[1]Additional unscheduled visits may occur (for example: to repeat a blood test, for additional clinical review)

[2]eDiaries are remotely monitored in (near) real-time for the occurrence of grade ≥3 AEs and daily for non-completion

[3]Minor differences in blood volumes may occur depending on the collection tubes and equipment used (~ = approximately); additional repeat blood draws may be required (for example, if there is a problem with the sample, result abnormality, or participant unwell)

[4] optional, at the discretion of the investigator

[5] optional for the participant

5 BACKGROUND & RATIONALE

5.1 Crimean-Congo Haemorrhagic Fever (CCHF)

In 1944, an outbreak of haemorrhagic fever occurred in Russian troops re-occupying the Crimean peninsula.[1] Cases of the disease were soon linked to tick exposure. The causative organism was identified in 1967, using suckling mice to cultivate the virus.[2,3] In 1969, it was realized that the virus was the same as a virus isolated in the Belgian Congo in 1956.[4] The disease has been referred to as Crimean-Congo haemorrhagic fever (CCHF) since the early 1970s.

The causative agent is an *Orthonairovirus* (genus *Nairoviridiae*, family *Bunyaviridales*), a negative-sense, single-stranded RNA virus. The virion is spherical, approximately 80-120nm in diameter. The outer membrane is studded with two glycoproteins, G_N and G_C. The virions contain three RNA genome segments: small (S), medium (M) and large (L). A precursor for the surface glycoproteins is coded by the M segment. The S segment encodes nucleoprotein; the L segment encodes an RNA-dependent RNA polymerase.[2]

The virus causes asymptomatic infection in many wild and domesticated vertebrates, including cattle, sheep, goats, camels and ostriches. It is usually transmitted by ixodid ticks, particularly those of the genus *Hyalomma*.[5] The northern limit of distribution of these ticks is approximately 50°N.[6,7] Transmission can also occur by contact with infected body fluids and tissues.[2]

Human infections have been reported in numerous countries in southern Europe, the Middle East, Africa and south-west Asia.[8,9] A few cases acquired by travellers from endemic countries have been diagnosed in the UK.[10] Turkey, Iran, Russia and Uzbekistan all report more than 50 cases per year. Recently, cases have been reported in Spain.[11] The WHO estimates that 3 billion people live in areas at risk, and that CCHF infects 10,000 to 15,000 people per year, causing 500 deaths.[7]

Serological surveys in high-risk areas of Turkey suggest that about 88% of human infections are subclinical.[12] In humans who develop disease, the incubation period may be from 1 to 13 days; typically, it is 1 to 5 days following a tick bite, or 5 to 7 days following exposure to infected blood or tissues. The disease is characterised by sudden onset fever, headache and myalgia; vomiting, abdominal pain and diarrhoea may also occur.[13] A haemorrhagic phase typically begins around 3 to 5 days later. Petechial skin rashes may progress to extensive subcutaneous ecchymoses; subconjunctival and other mucosal haemorrhages may occur; there may be bleeding from the gastrointestinal and urinary tracts; cerebral haemorrhage may also occur. In fatal cases, death is usually in the second week of the illness, from haemorrhage, shock and organ failure. High viral load (≥10^8 copies/ml) correlates with fatal outcome.[14]

Supportive therapy, including replacement blood products, is the mainstay of treatment.[13] Ribavirin has been observed to reduce viral load and lethality in laboratory suckling mice, but its efficacy in humans has not been definitively demonstrated in randomised clinical trials.[15] Specific immunoglobulin therapy has been used for post-exposure prophylaxis and treatment, but efficacy has not been confirmed by case-control studies.[15,16]

5.2 Rationale for vaccination

CCHF is one of twelve diseases currently listed by the WHO as a priority disease for research and development, based on its risk to public health, epidemic potential and inadequacy of countermeasures.[17] It is listed as a high consequence infectious disease by the UK Health Security Agency.[18]

Only one CCHF vaccine has been used in humans outside clinical studies. This was developed in the early 1970s by the Soviet Institute of Poliomyelitis and Viral Encephalitides. The vaccine was based on brain tissue from infected newborn laboratory mice and rats, inactivated by chemical and heat treatment.[19] This vaccine was approved by the Soviet Ministry of Health, and in 1974 it was licensed in Bulgaria for use in military, medical and agricultural workers over the age of 16 years in CCHFV-endemic areas. The number of cases of CCHF disease reported in Bulgaria in the 22 years after introduction of this vaccine was four-fold less than in the same time period before its introduction.[20] Factors other than vaccine efficacy may account for this observation, such as reduction in human exposure to ticks, reduction in infection rates in ticks and animals, or changes in reporting practices. Due to its mode of preparation and lack of regulatory data, this vaccine is very unlikely to gain widespread international acceptance.[9] It has not been licensed by the European Medicine Agency or the US Food and Drug Administration.

We have developed ChAdOx2 CCHF, a simian adenoviral-derived replication incompetent viral vector vaccine encoding the CCHF virus glycoprotein precursor. This vaccine could be used in the context of outbreaks or administered within routine national immunisation programmes. Its use could be targeted to high-risk areas or to individuals in high-risk occupations (*e.g.*, livestock farmers).[21]

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. An example of this is the ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine), developed by the University of Oxford, which has been shown to be safe, immunogenic and efficacious against COVID-19 disease in several clinical trials.[22-24] Over 2 billion doses have been administered.

One potential drawback to the use of adenoviral vector vaccines is that prior exposure to adenoviral antigens may lead to anti-vector immunity, dampening the potency of the vaccine.[25] Our study will therefore compare immune responses to ChAdOx2 CCHF in participants who have previously received an adenoviral-vectored vaccine with the responses in adenoviral-vectored vaccine naïve participants.

5.3 ChAdOx2 CCHF vaccine

5.3.1 ChAdOx2 vector and ChAdOx2 CCHF

ChAdOx2 is a recombinant simian adenovirus viral vector developed by the University of Oxford. It was derived from wild-type replication-competent isolate AdC68 (species adenovirus E, also known as SAdV-25 and Pan 9), which has been rendered replication-deficient through deletion of the E1/E3 gene region (which is essential for viral replication), with further modification to the E4 region. To produce ChAdOx2 CCHF, a human codon optimised gene encoding CCHFV glycoprotein under the control of the short cytomegalovirus promoter was inserted into the vector. The viral vector was then rescued and grown in the HEK293 derived TRex cell line, prior to CsCl purification and sterile filtration.

The CCHFV M segment gene codes for a glycoprotein precursor (GPC). After expression, this is processed by a range of proteases into five glycoproteins: MCL, GP38, Gn, NSm, and Gc. Of these glycoproteins, the Gn and Gc subunits show greatest conservation across CCHFV strains[26]. The Gn and Gc glycoproteins are the antigens found on the surface of CCHFV virus and are thought to be responsible for viral tropism and cell entry, though the cell surface target is unknown. Gn and Gc antigens have been shown to induce protective responses in some mouse challenge studies, and antibodies targeting Gc have been shown to neutralise CCHFV tec-VLPs (see Section 5.4).

The immunogenicity ChAdOx2 CCHF has been compared with a similar ChAdOx1-vectored vaccine (ChAdOx1- CCHFV GPC) in BALB/C mice.[26] Vaccination with ChAdOx2 CCHF induced significantly greater anti-CCHFV Gc antibody titres in mice than vaccination with ChAdOx1- CCHFV GPC, although no further significant differences were measured between vectors with regards to cellular or neutralisation responses induced by vaccination.

The safety and T-cell immunogenicity of a vaccine based on the ChAdOx2 platform (expressing four genes from the *Mycobacterium avium* subspecies *paratuberculosis*) has been assessed in humans, using a 'three-plus-three' dose escalation study design.[27] The vaccine was found to be safe and well tolerated in doses up to $5x10^{10}$vp. A rabies vaccine, ChAdOx2 RabG, has also been assessed in a phase I clinical trial, in which participants were sequentially allocated to receive low ($5x10^{9}$vp), middle ($2.5x10^{10}$vp) or high ($5x10^{10}$vp) doses.[28] Participants reported predominantly mild-to-moderate reactogenicity and there were no serious adverse events. The middle and high dose groups showed an encouraging immunogenicity profile, and at follow up one year after vaccination, 6/7 maintained a protective level of neutralising antibody.

5.3.2 ChAdOx2 CCHF pre-clinical studies

A version of ChAdOx2 CCHF (with intermediate early long CMV promoter) has been studied in immunocompetent (BALB/c) and immunodeficient (A129, IFNα/βR$^{-/-}$) mice (unpublished UK study).[29]

Four different vaccination schedules were compared:

- One dose of ChAdOx2 CCHF (given on D14): ChAd group
- One dose of MVA CCHF (given on D14): MVA group
- One dose of ChAdOx2 CCHF (on D0), followed 14 days later by one dose MVA CCHF (on D14): ChAd/MVA group
- Two doses of MVA CCHF, given 14 days apart (D0 and D14): MVA/MVA group

MVA CCHF is a vaccine using the viral vector modified Vaccinia virus Ankara (MVA).[30] Other pre-clinical studies in which this vaccine has been used are discussed in section 5.4.

Each dose of ChAdOx2 CCHF was $5x10^7$ infectious units (IU); each dose of MVA CCHF was $1x10^7$ plaque forming units (PFU). Immunogenicity testing was done 21 days after the final vaccination (D35). For the immunogenicity studies, there were eight BALB/c mice and four A129 mice in each group (with one group for each vaccination schedule and one control group). For the challenge studies, there were six A129 mice in each group.

The results from these studies are shown in the following Figures.

CCHFV Gc-specific humoral responses were observed in all groups of vaccinated mice. However, Gn-specific responses were generally not observed, apart from in the heterologous ChAd/MVA group (Figure 1).

Figure 1.

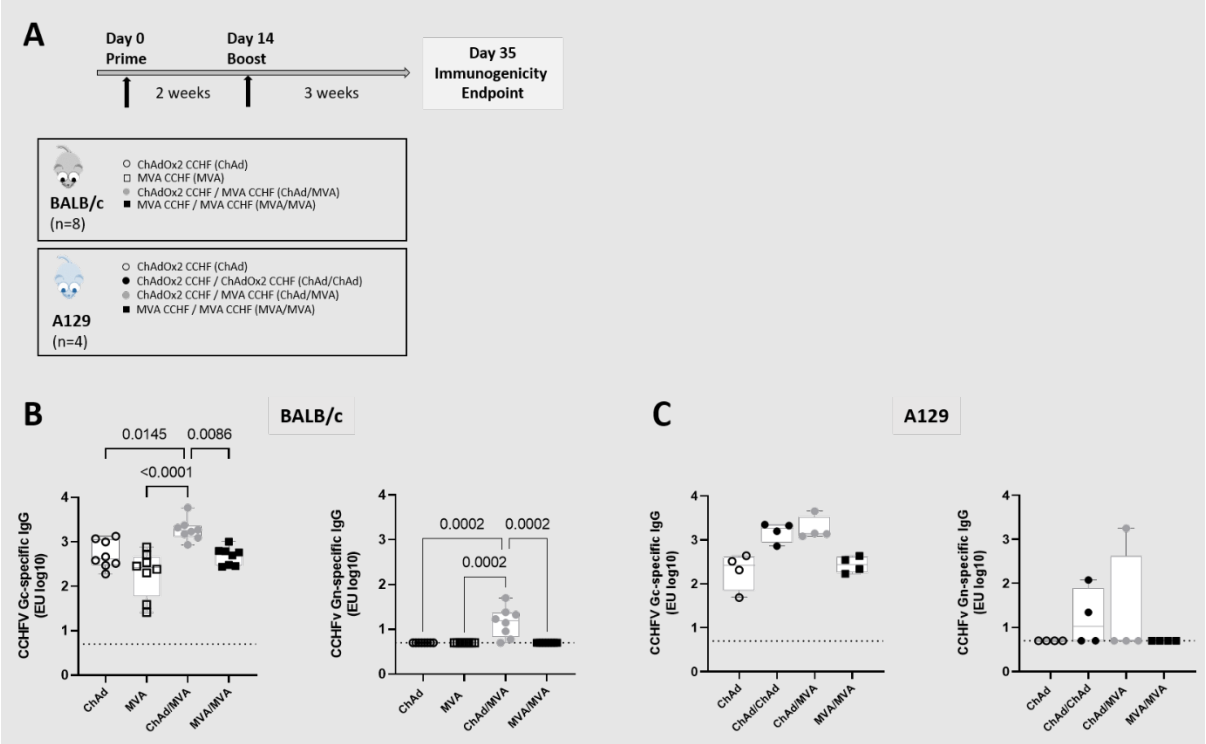


Figure 1. CCHFV-specific IgG responses following ChAd and MVA immunisation. Immunisation schedules of the two mouse strains **(A)**. Prime-boost regimens received prime vaccination on day 0 of experiment, and prime only regimens and prime-boost regimens received prime and boost vaccination respectively on day 14. Antibody responses were measured in the serum of BALB/c (n = 8) **(B)** and A129 (n = 4) mice **(C)** collected 3 weeks after the final immunization. CCHFV Gc-specific (left panel) and Gn-specific (right panel) IgG responses were quantified by standardised ELISA. Individual data points expressed as logarithmic ELISA units (EU log10) are shown here as a scatter dot plot with boxes showing the median and interquartile range and whiskers showing minimum and maximum. For (B, left panel) significant differences were determined by a one-way ANOVA with Tukey post-hoc analysis and data in graphs (B, right panel) and (C) analysed with Kruskal-Wallis test with Dunn's

correction for multiple comparisons between vaccination groups. Dotted lines represent the quantified level of response from control immunised mice.

Antibody neutralization capacity was evaluated by a pseudotype neutralization assay using CCHF transcription- and entry-competent virus-like particles (tecVLP) that have been shown to be morphologically similar to live CCHFV.[31] ChAd/MVA prime-boost immunisation induced significantly greater neutralization of tecVLPs entry compared to the ChAd prime only group. In BALB/c mice the neutralizing response was correlated with IgG antibody levels (Pearson r = 0.482, $P < 0.008$). Avidity of Gc-specific IgG was measured using a sodium thiosulfate displacement ELISA; it was lower in the ChAd prime only group than in the other vaccinated groups (Figure 2).

Figure 2

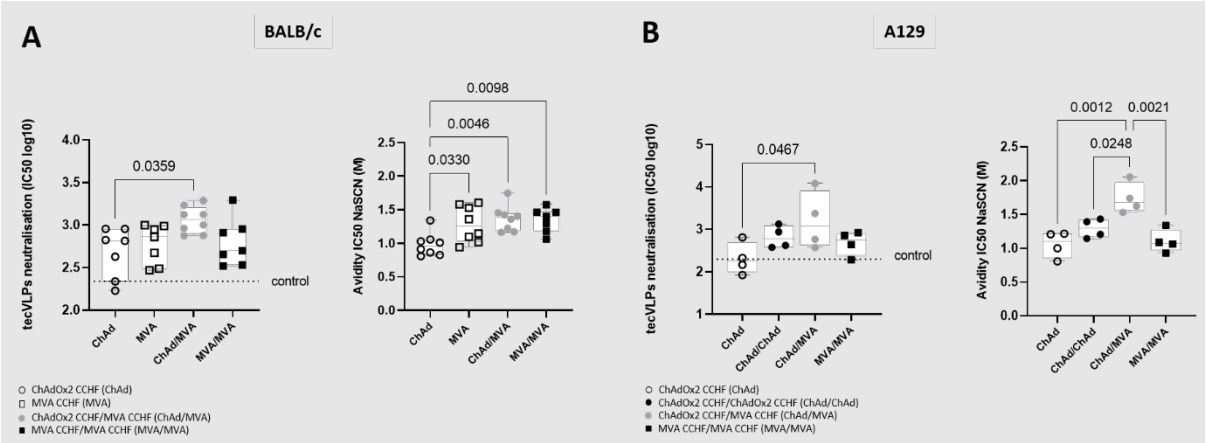


Figure 2. Measurement of CCHFV-specific antibody-mediated neutralisation and avidity. Antibody neutralisation responses and avidity were measured in the serum of **(A)** BALB/c (n = 8) and **(B)** A129 (n = 4) mice collected 3 weeks after the final immunization. Neutralisation was assessed by measuring inhibition of CCHFV tecVLPs entry into A549 cells, shown by individual data points expressed as logarithmic IC50 values (left panels). Avidity of CCHFV Gc specific IgG responses was measured using a NaSCN chemical displacement ELISA (right panels). Individual data points are shown here as a scatter dot plot with boxes showing the median and interquartile range and whiskers showing minimum and maximum. Significant differences were determined by one-way ANOVA with Tukey post-hoc analysis. Dotted lines represent the quantified level of response from control immunised mice.

Further characterisation of the CCHFV Gc-specific IgG response revealed a mixed profile of IgG subclasses in both mouse strains, with mainly IgG2a being induced in all animals across the immunisation regimens (Figure 3).

Figure 3.

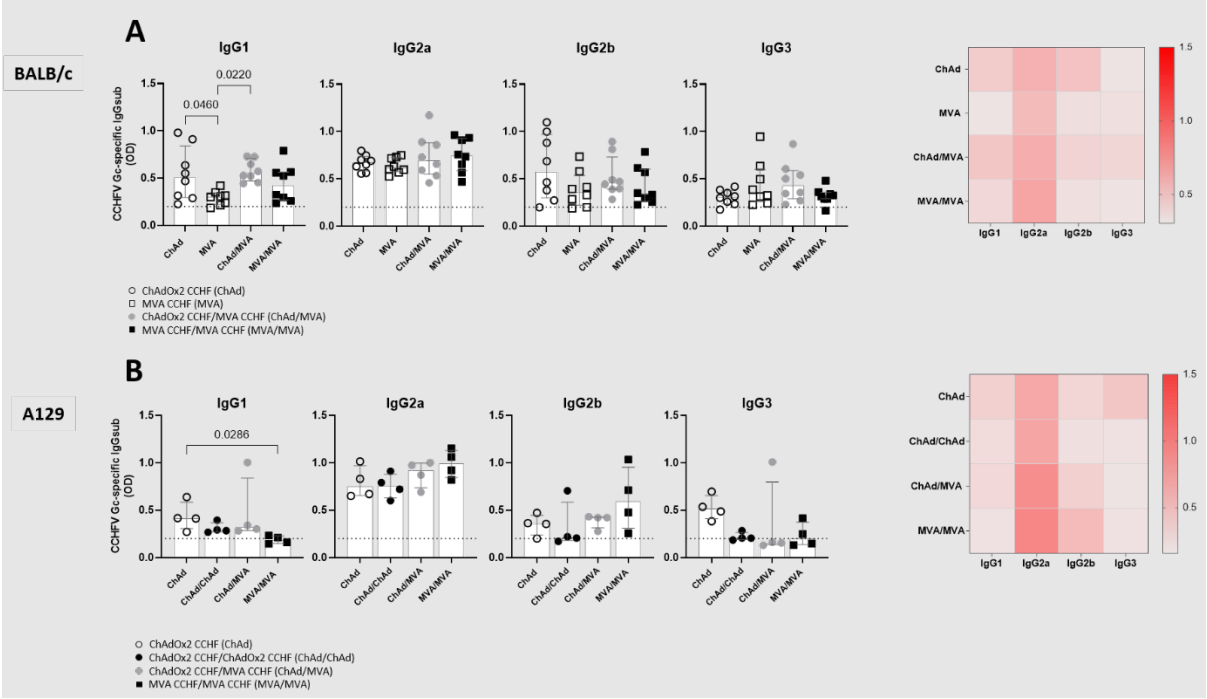


Figure 3. Detection of IgG subclasses in BALB/c and A129 mice immunised with ChAd and MVA regimens. Samples with detectable CCHFV Gc-specific responses were normalised and diluted to 1 EU. IgG subclasses were quantified by optical density and data displayed as scattered dot plots with bars showing the median and IQR, and as heatmap with median OD values of each group. Individual data points represent OD of a single mouse. BALB/c mice data (A) in each graph were analysed with a one-way ANOVA with Tukey post-hoc analysis, and A129 (B) data analysed with Kruskal–Wallis test followed by a post hoc Dunn's multiple comparison test to compare differences between vaccination groups. Dotted lines represent the assay limit of quantification.

In both mouse strains, all vaccine regimens induced CCHFV-specific cellular responses, measured in splenocytes by IFN-γ ELISPOT. In BALB/c mice, a single dose of ChAd induced a greater cellular response than a single dose of MVA or MVA/MVA prime and boost (Figure 4).

Figure 4.

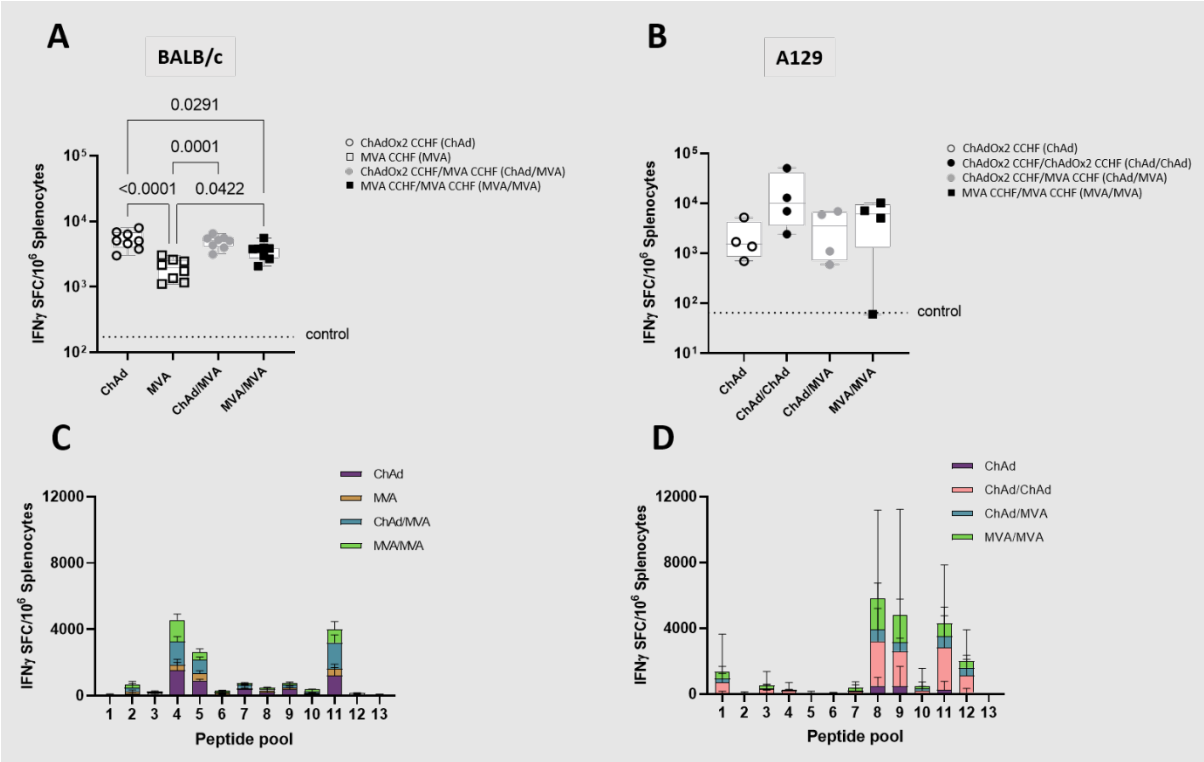


Figure 4. CCHFV-specific cellular responses in mice immunised with ChAd and MVA regimens. CCHFV antigen-specific IFN-γ responses in mouse splenocytes were assayed by IFN-γ ELISPOT assays. The summed IFN-γ ELISPOT responses in BALB/c (A) and A129 mice (B) are displayed as individual data points as a scatter dot plot with boxes showing the median and interquartile range and whiskers showing minimum and maximum. Responses to individual peptide pools are displayed by stacked bars of IFN-γ responses in BALB/c (C) and A129 mice (D), with lines showing the median with IQR. Significant differences were determined by one-way ANOVA with Tukey post-hoc analysis. Dotted lines represent the quantified level of response from control immunised mice. (Note that the second group in the A129 mice received ChAd/ChAd).

A129 mice (6 in each group) were challenged with a lethal dose of CCHFV IbAr10200 strain, 22 days after final immunisation. Controls showed clinical signs of disease and by day 5 post challenge were deemed to have met humane endpoints and euthanised. Following challenge, control mice displayed a raised body temperature during days 4 and 5 and a consistent sharp fall in body weight up to day 5. No mice immunised against CCHFV showed signs of temperature elevation; they recovered or stabilised weight after an initial minor loss post-challenge (Figure 5).

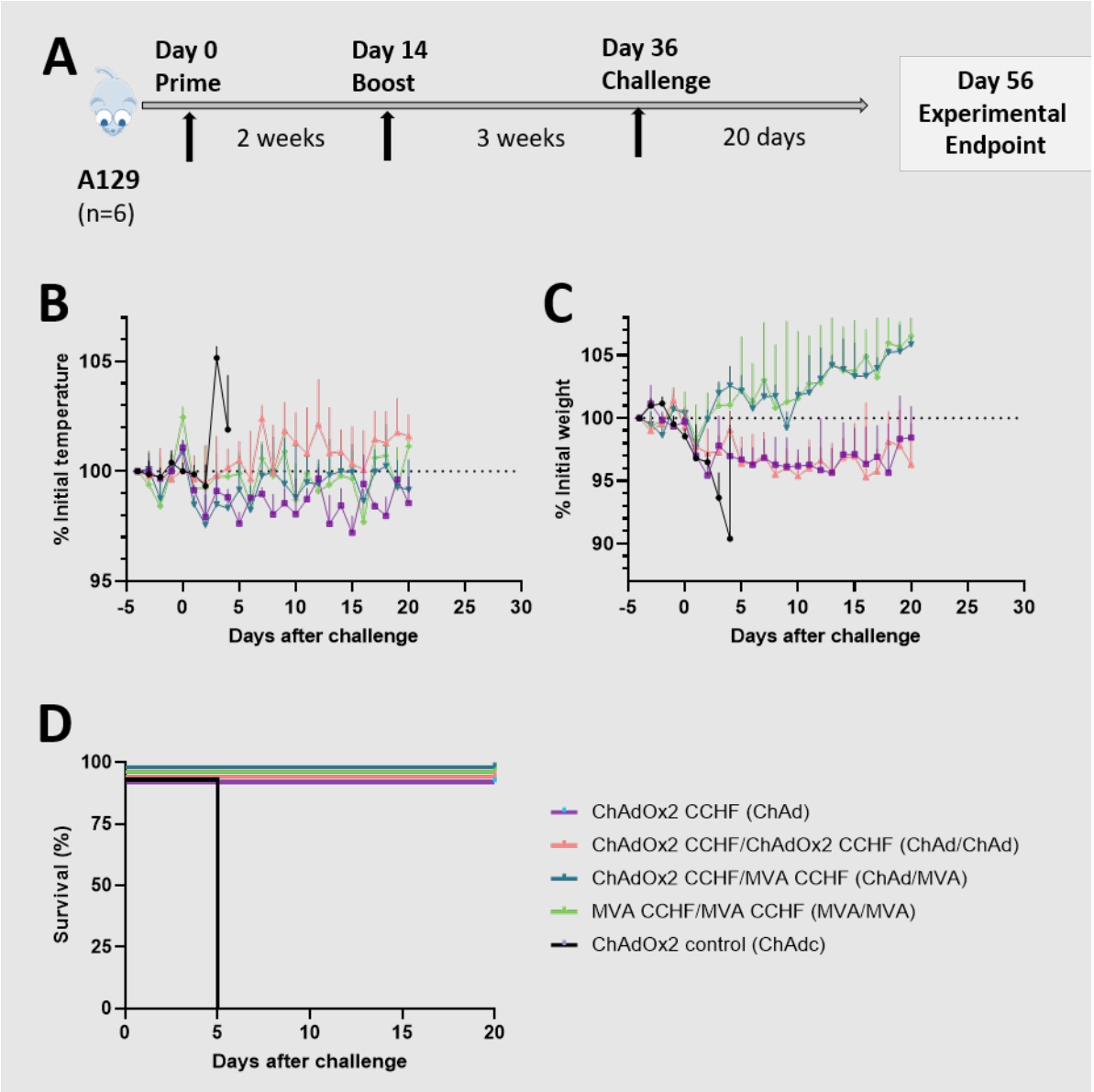


Figure 5. Assessing the protective effect of ChAd and MVA regimens against challenge with CCHFV in A129 mice. Challenge timeline overview **(A)** for A129 mice (n=6 mice per group). Mice in prime-boost regimens received prime vaccination on day 0 of experiment. Prime only regimens and prime-boost regimens received prime and boost vaccination respectively on day 14. Mice were challenged on day 36 with a 100µl volume of 200 ffu CCHFV that was intradermally administered. All surviving mice were euthanised on day 56. Following challenge, all mice were monitored for temperature **(B)** and weight **(C)** changes that are displayed as the recorded median of each regimen group with error

bars representing IQR, as well as Kaplan-Meier survival plot **(D)** displaying percentage survival up to 20 days post challenge.

Samples of blood, spleen and liver were collected from culled animals at the end of the study (20 days post challenge for vaccinated groups; 5 days post challenge for controls). The levels of CCHFV RNA were compared by RT-PCR and demonstrated that in the blood, spleen and liver there was an absence of viral RNA in all mice immunised against CCHFV, unlike ChAd control immunised mice that displayed high viral RNA in blood, spleen and liver (Figure 6).

Figure 6.

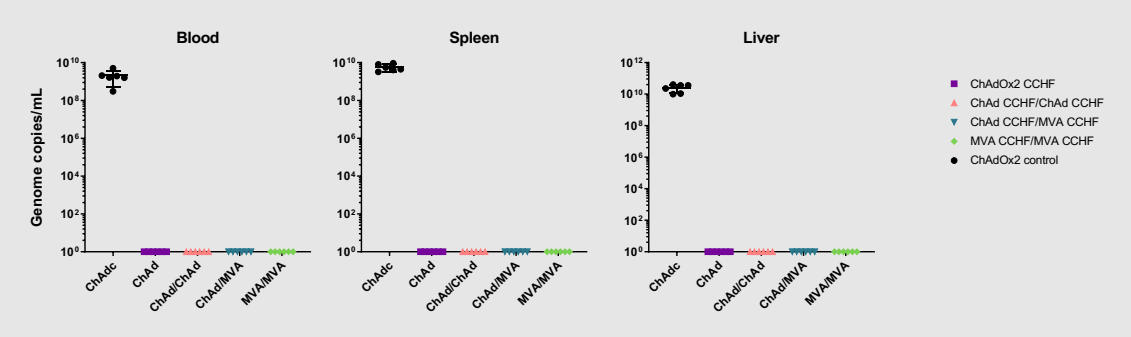


Figure 6. Viral RNA load in blood, liver and spleen, 5 days post viral challenge for control group, 20 days post viral challenge for other groups.

Liver and spleen samples from all animals were analysed for histology and detection of viral antigen by immunohistochemistry. Microscopic lesions associated with CCHFV infection were observed in the spleen and liver of all control animals. Pathology observed in the spleens of control mice included the infiltration of the parenchyma by macrophages in the red pulp, and lymphocyte loss and apoptosis in the white pulp, characterised by lymphocyte paucity, apoptotic bodies and tingible body macrophages. In the livers of control mice, microscopic changes comprised multiple, small foci of hepatocyte necrosis, consisting of cytoplasmic eosinophilia and loss of nuclear detail accompanied by a variable inflammatory cell infiltration, primarily neutrophilic cell infiltrate, with scattered macrophages.

The spleen and liver of all animals receiving immunisation against CCHFV were normal with no CCHF-associated microscopic lesions. Minimal to moderate inflammatory changes were observed in the livers of some immunised mice, although the significance of this is not clear.

The spleen and liver of all control mice displayed the presence of strongly staining viral antigen. In contrast, all animals immunised against CCHFV displayed no viral antigen in the spleen or liver following immunohistochemical staining.

5.3.3 ChAdOx2 CCHF clinical studies

To date, there have been no clinical studies of ChAdOx2 CCHF and therefore the proposed study is a first-in-human study.

5.4 Other CCHF vaccines in pre-clinical testing

In the last decade, CCHF vaccine development has focused on the viral glycoproteins and nucleoprotein.[21] These proteins produced either *in vitro*, in cell cultures, or *in vivo*, using vectors to deliver genes encoding CCHFV antigens, thus directing endogenous protein production. The latter approach may be preferable, since the proteins acquire post-translational modifications, as they would in natural infection.[32] The viral glycoproteins have received most attention as they are located on the virion surface and seem most likely to stimulate production of neutralizing antibody.

Good animal models for the evaluation of candidate vaccines require selection of animals which are immunocompetent, permitting assessment of immune responses to vaccination; however, the animals should also be susceptible to disease, allowing protection provided by vaccination to be assessed in challenge studies. Most animals do not develop disease when infected with CCHF virus, and so cannot be used for viral challenge testing. Pre-clinical testing of candidate CCHF vaccines has generally been carried out using mouse models. Certain strains of knockout mice with deficiencies of interferon signalling, including STAT-1$^{-/-}$ and INFAR$^{-/-}$, succumb to CCHFV infection within 5 days; these have been used extensively in the evaluation of potential CCHF vaccines. The disadvantage of these models is that they do not closely recapitulate the human immune system. Recently, it has been shown that cynomolgus macaques infected with CCHFV Kosova Hoti exhibit patterns of clinical disease very similar to those seen in humans.[33] This non-human primate model provides an alternative to mouse models to assess candidate CCHF vaccines.

A wide variety of strategies have been used to develop CCHF vaccines. These have been reviewed by Tipih and Burt.[21]

Insect expression technology was used to produce glycoproteins Gc and Gn in Drosophila. The vaccine derived using this method stimulated neutralising antibody in mice, but it was not protective against viral challenge.[34]

Genetically modified tobacco plants expressing the envelope glycoproteins Gn and Gc were fed to BALB/c mice, eliciting specific IgG. However, the neutralizing capacity of the induced antibody was not assessed.[35]

Transcriptionally active virus-like particles have been developed using reverse genetics. These consist of a genome and nucleoproteins surrounded by a membrane displaying surface glycoproteins. Vaccines produced using this technology induce neutralizing antibodies in IFNAR$^{-/-}$ mice and protect against viral challenge.[36-38]

A new conventional naked mRNA vaccine expressing the more conserved small (S) segment of the Ank-2 strain of CCHF virus elicited the production of anti-nucleocapsid (N) specific immune responses but did not elicit neutralising antibodies. Two doses provided protection against viral challenge in IFNα/β/γR$^{-/-}$ mice.[39]

Several DNA vaccines have been studied in mouse models. In the first of these published, a DNA vaccine expressing the entire CCHFV M-segment elicited neutralizing antibody in some mice but was described as "not very immunogenic".[40] No viral challenge model was available when this study was conducted. Another DNA vaccine expressing the M-segment was studied in two mouse models.[41] Three vaccinations elicited neutralizing antibody and provided 60-70% protection against lethal challenge. A DNA vaccine encoding the CCHFV nucleoprotein stimulated NP-specific antibody, although this did not have neutralizing capacity.[42] The vaccine protected IFNAR$^{-/-}$ mice from lethal challenge. Co-administration of an adjuvant, cluster differentiation 24 (CD24), enhanced the immunogenicity of the vaccine.

A DNA-based vaccine, containing two plasmids encoding the glycoprotein precursor and nucleoprotein of CCHFV, has been evaluated in cynomolgus macaques.[43] The vaccine elicited strong CCHF-specific antibody and T-cell responses. Six vaccinated macaques developed significantly lower viral loads in blood and tissues, and lower levels of disease markers, following CCHFV challenge than six sham-vaccinated controls.

An inactivated vaccine has been prepared by propagating the CCHFV Turkey-Kelkit06 strain in cell culture and inactivating with formaldehyde.[44] Two doses of 20µg or 40µg of this vaccine elicited neutralizing antibody; three doses provided 80% protection against lethal viral challenge.

Several viral-vectored CCHF vaccines have been investigated. An attenuated poxvirus vector, modified Vaccinia virus Ankara (MVA), has been used as the platform for two CCHF vaccines, one expressing the virus glycoproteins and another expressing the nucleoprotein.[30,45] Both vaccines evoked cellular and humoral immune responses, but only the vaccine expressing the viral glycoprotein protected against viral challenge. A vaccine based on human adenovirus 5, expressing the CCHFV nucleoprotein, provided partial protection in challenge studies.[46] A replication competent recombinant vesicular stomatitis virus (VZV) expressing the CCHFV glycoprotein precursor provided 100% protection against a lethal viral challenge after a single vaccine dose.[47] Two vaccinations of a viral-vectored vaccine based on bovine herpes virus type 4, encoding CCHFV nucleoprotein, provided complete protection to viral challenge in IFNAR$^{-/-}$ mice.[48]

5.5 Other CCHF Vaccines in clinical testing

The International Clinical Trials Registry Platform was searched on 18th November 2022 for "Crimean-Congo". One experimental CCHF vaccine in a phase I clinical trial was identified. This is shown in Table 4 CCHF Vaccines in Registered Clinical Trials (18th November 2022). The trial is being conducted in Southampton, using a vaccine based on the attenuated viral vector modified vaccinia virus Ankara, which has been developed at the UKHSA. It is still recruiting. There are no published clinical data on CCHF vaccines, other than the vaccine developed in the 1970s by the Soviet Institute of Poliomyelitis and Viral Encephalitides, described in Section 5.2.

Table 4 CCHF Vaccines in Registered Clinical Trials (18th November 2022)

Vaccine technology	Vaccine Name	Manufacturer	Trial Phase	Registration number, year of registration	Results
Attenuated viral vector (modified Vaccinia virus Ankara)	MVA-CCHF		Phase 1	ISRCTN14935155 2021	Not available (trial recruiting)

In addition, a Turkish phase I study was posted on ClinicalTrials.gov (NCT03020771) on 13 January 2017. This aimed to evaluate KIRIM-KONGO-VAX, an inactivated CCHF vaccine (prepared in cell culture and inactivated with formalin) in 60 participants. Recruitment is complete, but results have not been reported.[49]

5.6 Previous clinical experience with other ChAdOx2-vectored vaccines

Two phase I trials of ChAdOx2-vectored vaccines have taken place, both conducted in the UK.

Table 5 ChAdOx2 Vaccines in clinical-phase development

IMP	Indication	First clinical trial application date (trial registration number)
ChAdOX2 MAP	Mycobacterium avium subspecies paratuberculosis	03/03/2020 (ISRCTN36126048)
ChAdOx2 RabG	Rabies	14/11/2019 (NCT04162600)

ChAdOx2 MAP, which expresses four genes from the *Mycobacterium avium* subspecies *paratuberculosis*, was assessed in a phase 1 trial of 12 participants, using a 'three-plus-three' dose escalation study design.[26] The first 3 participants received ChAdOx2 HAV 5×10^9 vp, and the next 3 volunteers received a dose of 2.5×10^{10} vp. None of these participants presented either severe or serious adverse reactions, and so a further 6 participants were vaccinated with 5×10^{10} vp. The safety data from this study are shown in Figure 7. T-cell responses to all four antigens were detected at day 28 post-vaccination, and these were greatest in the group receiving a dose of 2.5×10^{10} vp.

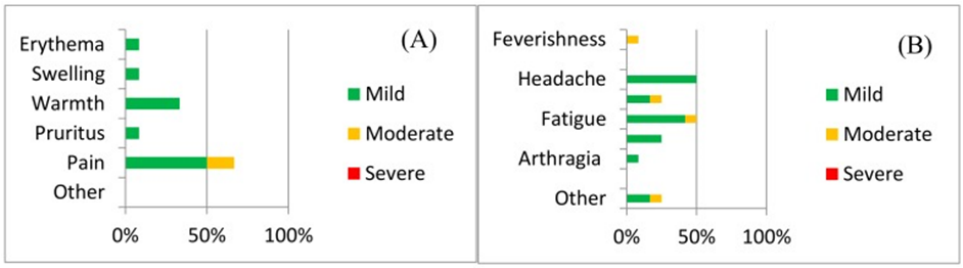


Figure 7. Safety data for ChAdOx2 HAV: The frequency of adverse reactions following vaccination with ChAdOx2 HAV is shown, with severity indicated by shading. (**A**) Local adverse reactions and (**B**) systemic adverse reactions. Data represent adverse reactions from all 12 volunteers across all three doses.

ChAdOx2 RabG, a rabies vaccine, has also been assessed in a similarly designed phase I clinical trial, in which participants were sequentially allocated to receive low (5 x 10^9 vp), middle (2.5 x 10^{10} vp) or high (5 x 10^{10} vp) doses.[27] There were 3 participants in each of the low and middle dose groups, and 6 in the high dose group. Participants reported predominantly mild-to-moderate reactogenicity and there were no serious adverse events (Figure 8). The middle and high dose groups showed an encouraging immunogenicity profile, and at follow up one year after vaccination, 6/7 maintained a protective level of neutralising antibody.

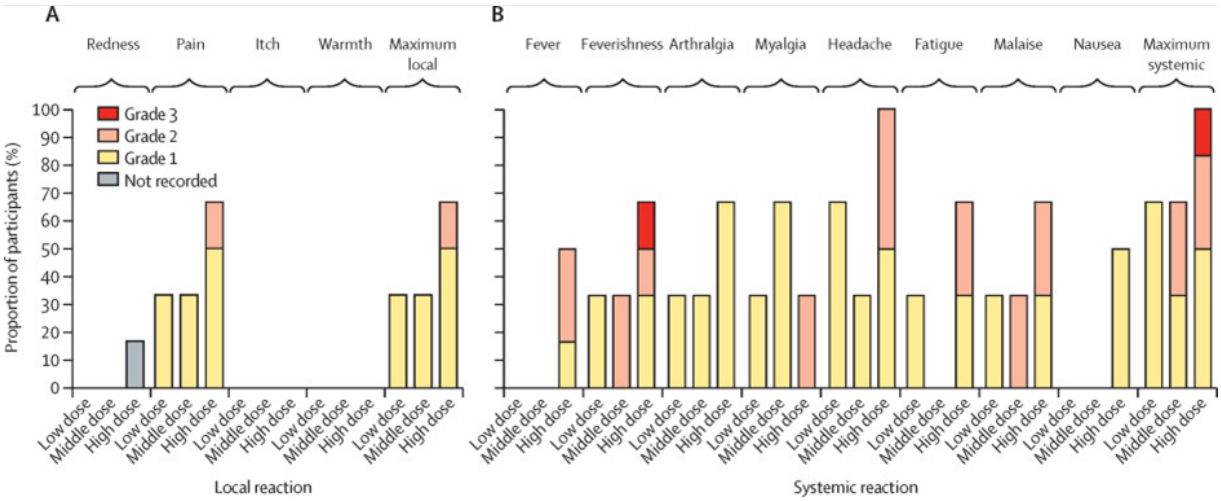


Figure 8: Solicited adverse events following vaccination with ChAdOX2 RabG.

For each of the individual-solicited local (A) and systemic (B) reactions, the maximum severity reported by each volunteer over the 7 days after vaccination is shown. In addition, to provide a global view of reactogenicity, the highest graded of all local and all systemic reactions is shown for each volunteer.

5.7 Previous clinical experience with other ChAdOx1-vectored vaccines

ChAdOx1 is a replication incompetent adenovirus vector derived from wild type Chimpanzee adenovirus serotype Y25. ChAdOx2 is derived from another species E adenovirus, serotype C68 (AdC68, also known as SAdV25). Serotype Y25 and C68 share a close phylogenetic relationship, determined by analysis of nucleotide sequences of the hexon and fibre proteins. It may therefore be

anticipated that ChAdOx1- and ChAdOx2-vectored vaccines are likely to share similar safety and immunogenicity profiles.

To date, clinical trials have been conducted with 17 ChAdOx1 vaccines expressing different inserts that target either viral, bacterial, parasitic or cancer antigens (Appendix C). The most notable of these is ChAdOx1 nCoV-19, which has been authorised for use in many countries and has been used widely. Over 2 billion doses have been administered worldwide.[48-52] Clinical trial and post-marketing experience with ChAdOx1 nCoV-19 has shown the vaccine to be well-tolerated, safe and effective against COVID-19. Serious side effects with ChAdOx1 nCoV-19 are extremely rare. The safety of ChAdOx1 nCoV-19 during pregnancy has been examined in clinical trial participants and a post marketing study. An analysis of pregnancies across ChAdOx1 nCoV-19 clinical trials included 72 pregnancies in ChAdOx1 nCoV-19 recipients and found no evidence of adverse pregnancy outcomes.[60]

Other ChAdOx1-vectored vaccines that have been assessed in early phase clinical trials include vaccines for influenza (encoding the fusion protein NP+M1), tuberculosis (85A), prostate cancer (5T4), malaria (LS2), chikungunya (structural polyprotein), zika (prM and E), group B meningococcus (outer membrane protein), Middle East Respiratory Syndrome coronavirus (spike protein), ebola (Zaire and Sudan surface glycoproteins), and others. These trials have yielded positive safety and immunogenicity results.[53,54] Many of these trials have been sponsored by the University of Oxford (Appendix D). A trial for a new vaccine against Nipah virus, ChAdOx1 NipahB, is currently being instigated.

5.8 Rationale for selected doses

The regimen and dose of ChAdOx2 CCHF (5 x 10^{10} viral particles per dose, as a 2-dose administration) was selected on the basis of clinical experience with other ChAdOx1- and ChAdOx2-vectored vaccines, as well as other adenovirus vaccines (such as ChAd63).

ChAdOx1 nCoV-19 has been approved as a 2-dose schedule, administered 4 to 12 weeks apart, at a dose of 5 x 10^{10} viral particles per dose (or equivalent). This regimen is well tolerated and immunogenic. Although approved as a 2-dose schedule, the vaccine is immunogenic following the first dose.[33] The second dose significantly boosts binding and neutralising antibody responses to SARS-CoV-2. A 12-week interval between doses results in superior immunogenicity to a 4-week interval. The second dose produces lower rates of adverse reactions compared to the initial dose.[50-52] Studies have demonstrated its efficacy following both a single and two-dose regimen.

Many clinical trials of ChAdOx1-vectored vaccines have included doses up to 5 x 10^{10} viral particles (see Appendix D). In every case, the safety and immunogenicity profiles were acceptable.

Two vaccines based on the ChAdOx2 platform have been assessed in phase 1 trials and found to be safe and well tolerated in doses up to 5x10^{10}vp (see Section 5.6).[27,28]

Based on these data, this study will use a 2-dose regimen of ChAdOx2 CCHF, each containing 5 x 10^{10} vp, given at a 12-week interval.

5.9 Potential risks to participants

Trial related risks are summarised below. Potential risks associated with ChAdOx2 CCHF are also discussed within the ChAdOx2 CCHF Investigator Brochure.

5.9.1 Risks related to ChAdOx2 CCHF

The most likely side effects that recipients of ChAdOx2 CCHF may experience are short-lived local (primarily injection site tenderness or pain) and systemic vaccine reactions (fatigue, headache, malaise, feverishness) that resolve completely within days.

There has been a far wider clinical experience with ChAdOx1- than with ChAdOx2-vectored vaccines, particularly with ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine). As noted above in Section 5.7, because of the close similarity between these two platforms, it may be anticipated that ChAdOx1- and ChAdOx2-vectored vaccines are likely to share similar safety profiles.

The frequency of the commonest adverse reactions to ChAdOx1 nCoV-19 are shown in Table 6 below.

Table 6: Frequency of commonest adverse reactions to ChAdOx1 nCoV-19[53]

Adverse Reaction	Frequency (%)
Injection site tenderness	68%
Injection site pain	58%
Fatigue	53%
Headache	53%
Malaise	44%
Myalgia	44%
Feverishness	34%
Arthralgia	27%
Nausea	22%
Fever over ≥38°C	8%

Rarer adverse reactions associated with ChAdOx1 nCoV-19 are shown in Table 8, Section 11.2.

Post-marketing experience with ChAdOx1 nCoV-19 has revealed a very rare but serious side effect following vaccination with ChAdOx1 nCoV-19 (which has also been associated with the adenovirus-vectored Johnson & Johnson COVID-19 vaccine). This is known as thrombosis with thrombocytopenia syndrome (TTS) or vaccine-induced immune thrombotic thrombocytopaenia (VITT). It can present with venous thrombosis, often at unusual sites, such as cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis.[54] The condition can also present with arterial thrombosis.[55]. It can lead to death or serious long-term disability.

There has been marked geographical variation in the reporting rates of TTS/VITT. The WHO Strategic Advisory Group of Experts (SAGE) noted reporting rates have been far lower outside of the UK and EU, despite the widespread use of the vaccine in many countries outside of Europe.[56] An analysis of the AstraZeneca global safety database has shown reporting rates (in the 21 days after vaccination) vary, with 17.6 cases per million doses in Nordic countries, 10.0 cases per million doses in the UK and 0.2 cases per million doses in Brazil, South Korea and the Philippines.[57]

A review of 170 definite and 50 probable cases of VITT in the UK found a case mortality rate of 22%.[55] Most cases occurred between 5 and 30 days after vaccination (median 14 days, maximum 48 days). The age range was 18 to 79 years (median, 48), with no sex preponderance and no identifiable medical risk factors. Another UK study of over 3.7 million recipients of ChAdOx1 nCoV-19 found that after the first dose there was an increased risk of venous thromboembolism (standardized incidence ratio: 1.12 [95% CI: 1.05 to 1.20]), and of cerebral venous sinus thrombosis (standardized incidence ratio: 4.14 [95% CI: 2.54 to 6.76]).[58] Up to 23 November 2022, the MHRA had received Yellow Card reports of 445 cases of major thromboembolic events with concurrent thrombocytopenia in the UK following vaccination with ChAdOx1 nCoV-19 (221 in females, and 219 in males; age range from 18 to 93 years).[59] Fifty-one of the 445 reports have been reported after a second dose. The overall case fatality rate was 18% with 81 deaths, six of which occurred after the second dose. Cerebral venous sinus thrombosis was reported in 161 cases (average age 46 years) and 284 had other major thromboembolic events (average age 54 years) with concurrent thrombocytopenia. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered in the UK by 23 November 2022 was 24.9 million and the estimated number of second doses was 24.1 million. The reported incidence of major thromboembolic events with concurrent thrombocytopenia following the first dose was higher in the younger adult age groups compared to the older groups (21.8 per million doses in those aged 18-49 years compared to 11.3 per million doses in those aged 50 years and over). This contrasts with incidence of these events after the second dose, which were commoner in the older age group (1.0 per million doses in those aged 18-49 years compared to 2.1 per million doses in those aged 50 years and over).

It is widely recognised that VITT is more likely to occur after a first dose of ChAdOx1 nCoV-19 than after a second dose. An international consortium has set up a registry which provides data on cases of cerebral venous sinus thrombosis occurring within 28 days of ChAdOx1 nCoV-19 vaccination. Of the 124 cases, 120 were after a first dose (61 definite, 20 probable, 10 possible, and 29 unlikely VITT), and 4 were after a second dose (1 definite, 1 probable, 1 possible, and 1 unlikely VITT).[60] The interval between receiving the second vaccine dose and symptom onset varied between 1 and 6 days.

Cerebral venous sinus thrombosis (CVST) has been the most closely monitored manifestation of VITT. Using data from the European Medicines Agency's EudraVigilance database (until June 13, 2021), the absolute risk of cerebral venous sinus thrombosis (CVST) within 28 days of first-dose vaccination with ChAdOx1 nCoV-19was estimated to be 7.5 per million (95% CI: 6.9-8.3).[61] In an age-stratified analysis, the absolute risk was the highest in the 18- to 24-year-old group (total CVST 11.0 per million [95% CI 5.0–23.9]). In the age groups 60 to 69 years and ≥70 years, the risk of CVST was the lowest (2.2 per million (95% CI 1.4–3.3) and 1.3 per million (95% CI 0.6–2.9), respectively).

The pathophysiological mechanism behind VITT appears to be activation of platelets by antibody to platelet factor 4 (PF4).[62,63] This closely resembles the pathophysiology of heparin-induced thrombocytopenia, which is also caused by anti-PF4 antibodies.

Other very rare serious reactions have been identified as part of post-marketing surveillance of ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine). These include anaphylaxis, Guillain-Barré syndrome (GBS), transverse myelitis, capillary leak syndrome (CLS), and immune thrombocytopenic purpura (ITP). By 1st December 2022, the Yellow Card reporting system had received 888 reports of anaphylaxis or anaphylactoid reactions, 514 reports of suspected Guillain-Barré syndrome, 129

reports of transverse myelitis and 18 reports of capillary leak syndrome, after about 50 million doses of ChAdOx1 nCoV-19. The risk of ITP is about 5 cases per million doses of the vaccine.[59]

It is currently unknown whether these very rare reactions will occur with other ChAdOx1- or ChAdOx2-vectored vaccines. As ChAdOx2 CCHF has similarities to ChAdOx1 nCoV-19, participants will be informed about these conditions as part of the informed consent process for the trial. Investigators will be aware of potential signs of these conditions.

Given existing safety data which supports the use of ChAdOx1 nCoV-19 use in pregnant women, there is no reason to believe ChAdOx2 CCHF would be harmful to women or the foetus during pregnancy. However, there are no data on the use of ChAdOx2 CCHF in pregnancy. Therefore, pregnant women will be excluded from the trial and participants of childbearing potential will be required to use effective contraception (see section 8.3).

5.9.2 Other 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 taken by regular blood donors over the same period, so should not compromise healthy participants (for comparison, a *single* donation to the NHS blood bank would be approximately 470ml). Intramuscular injections carry a risk of bleeding in patients with very low platelet counts or coagulopathies. A baseline full blood count (with a platelet count) taken prior to vaccination reduces this risk.

The medical tests carried out during the trial screening and follow up have the potential to find incidental medical problems that may require referral of volunteers for further investigation. Participants will be informed of these, and, with their consent, their general practitioner (GP) will be contacted.

5.10 Potential benefits to participants

The recruitment population will not directly benefit from participation in the study. This is because the individual's risk of becoming infected with CCHF is currently low. Furthermore, ChAdOx2 CCHF clinical efficacy against CCHF 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 CCHF infection following participation in this study. No specific additional medical care will be provided through participation, and medical procedures are performed with the aim of determining eligibility and safety during the trial.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives, outcome measures and evaluation timepoints

Outcome	Objective	Outcome measure	Evaluation timepoints[1]
Primary	To assess the safety and tolerability of ChAdOx2 CCHF in healthy volunteers	a) Occurrence of solicited local reactogenicity signs and symptoms	7 days following each vaccination (D0 to D7; V2 to V2+7)
		b) Occurrence of solicited systemic reactogenicity signs and symptoms	7 days following each vaccination (D0 to D7; V2 to V2+7)
		c) Occurrence of unsolicited adverse events (AEs)	28 days following each vaccination (D0 to D28; V2 to V2+28)
		d) Occurrence of abnormal safety laboratory measures	Cohort 1: D0, D2, D7, D14, D28, D56, V2, V2+2, V2+7, V2+14, V2+28, V2+56, V2+140, V2+280 Cohort 2: D0, D1, D14, D28, V2, V2+1, V2+14, V2+28, V2+140, V2+280
		e) Occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs)	Whole duration of the study (D0 to V2+280)
Secondary	To assess the immunogenicity of ChAdOx2 CCHF vaccine in healthy adult volunteers (at key timepoints)	Anti-CCHF glycoprotein specific serological response	Cohort 1: D0, D28, V2, V2+28 Cohort 2: D0, D28, V2, V2+28
	To compare the immunogenicity of ChAdOx2 CCHF vaccine in individuals previously vaccinated with a ChAdOx vaccine with ChAdOx naïve individuals (at key timepoints)	Anti-CCHF glycoprotein specific serological response	Cohort 1: D0, D28, V2, V2+28 Cohort 2: D0, D28, V2, V2+28
Exploratory[2]	To assess the immunogenicity of ChAdOx2 CCHF vaccine in healthy adult volunteers	a) Anti-CCHF glycoprotein specific serological response	Cohort 1: D14, D56, V2+14, V2+56, V2+140, V2+280 Cohort 2: D1, D14, V2+1, V2+14, V2+140, V2+280
		b) CCHF glycoprotein T cell response measured by IFN-γ ELISPOT	Cohort 1: D0, D14, D28, D56, V2, V2+14, V2+28, V2+56, V2+140, V2+280 Cohort 2: D0, D1, D14, D28, V2, V2+1, V2+14, V2+28, V2+140, V2+280
	To compare the immunogenicity of ChAdOx2 CCHF vaccine in	a) Anti-CCHF glycoprotein specific serological response	Cohort 1: D14, D56, V2+14, V2+56, V2+140, V2+280 Cohort 2: D1, D14, V2+1, V2+14, V2+140, V2+280

	individuals previously vaccinated with a ChAdOx vaccine with ChAdOx naïve individuals	b) CCHF glycoprotein T cell response measured by IFN-γ ELISPOT	Cohort 1: D0, D14, D28, D56, V2, V2+14, V2+28, V2+56, V2+140, V2+280 Cohort 2: D0, D1, D14, D28, V2, V2+1, V2+14, V2+28, V2+140, V2+280
	Immunological profiling	a) CCHF virus neutralising antibodies (using pseudoneutralization assays) b) Cellular immune response to CCHF virus measured by ICS, proliferation and/or whole blood assays c) Further immunological profiling	Timepoints will be detailed in the laboratory analysis plan
	To assess anti-vector immunity following vaccination	Binding and/or neutralising antibody responses against ChAdOx1	Timepoints will be detailed in the laboratory analysis plan
	To investigate the relationship between the composition of the gut microbiota, vaccination and immunological outcomes	Characterisation of the gut microbiome composition and function	D0, D14, V2+14, V2+281

[1]Visit and procedure timepoint windows are defined in section 0 (Schedule of Procedures).
[2]For any exploratory endpoints not completed prior to the end of the trial, where appropriate consent is received, samples will be transferred to OVC Biobank and analysed under the auspices of the OVC Biobank protocol and its ethical approval. (OVC Biobank HRA South Central - Hampshire B Research Ethics Committee, 21/SC/0161)

7 STUDY DESIGN

This is a multi-site, first-in-human, phase 1 trial to assess the safety, tolerability and immunogenicity of two doses of an intramuscular (IM) ChAdOx2 CCHF vaccine in healthy adults aged 18 to 55 years. There will be an initial lead-in cohort (Cohort 1) of 6 participants, followed by a cohort of 40 participants (Cohort 2), divided into two groups according to whether the participant has previously received a ChAdOx vaccine (Group A) or is ChAdOx vaccine naïve (Group B). All participants will receive two doses of ChAdOx2 CCHF, 12 weeks apart. All participants for cohort 1 will be recruited at the Oxford site; participants for cohort 2 may be recruited across any recruiting sites. The study is open-label and will not involve randomisation.

Volunteers will be recruited and vaccinated at the designated study sites.

7.1 Study Groups

Cohort	Group	Number of participants	Age	Previous ChAdOx vaccination	Intervention 1 (Week 0)	Intervention 2 (Week 12)	Follow-up
1		6	18-55	Either yes or no	5×10^{10} vp ChAdOx2 CCHF	5×10^{10} vp ChAdOx2 CCHF	1 year
2	A	20	18-55	Yes	5×10^{10} vp ChAdOx2 CCHF	5×10^{10} vp ChAdOx2 CCHF	1 year
	B	20	18-55	No	5×10^{10} vp ChAdOx2 CCHF	5×10^{10} vp ChAdOx2 CCHF	1 year

7.2 Trial duration

The total duration of the study will be 12 months from the day of enrolment for each volunteer. Participants will be considered enrolled into the trial at the point of their first vaccination.

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 Cohort and Group allocation

The first 6 participants recruited to the trial will be enrolled to Cohort 1.

All subsequent participants (n=40) will be recruited into Cohort 2. These participants will be divided into two groups, according to whether they have previously received a ChAdOx1- or ChAdOx2-vectored vaccination (Group A) or whether they are ChAdOx vaccine naïve (Group B). Recruitment into Cohort 2 will only proceed following the safety review detailed in section 11.19.

Participants in Cohort 2 will be assigned to Group A if they have received a ChAdOx1- or ChAdOx2-vectored vaccine 6 months or more before the first study vaccination. Previous immunisation with a ChAdOx1- or ChAdOx2-vectored vaccine within 6 months of the planned first study vaccination visit is a temporary exclusion criterion (see Section 8.2).

Participants in Cohort 2 will be assigned to Group B if they have never received a ChAdOx1- or ChAdOx2-vectored vaccine.

For a list of ChAdOx1- and ChAdOx2-vectored vaccines, see Appendix C.

Cohort 2 participants will be recruited to both groups until either Group A or Group B has enrolled 20 participants. Thereafter, participants will only be recruited to the other group, until that group has enrolled its target of 20 participants.

7.5 Blinding

This study will be open label.

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

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

1. Adults aged between 18 to 55 years (inclusive).
2. In good health as determined by
    a. Medical history
    b. Physical examination
    c. Clinical judgement of the Investigators
3. Able to attend the scheduled visits and to comply with all study procedures, including internet access for the recording of electronic diary cards.
4. Willing and able to give informed consent for participation in the study.
5. Agree to allow study staff to contact his or her GP or equivalent NHS databases to access the participant's vaccination records, medical history and have their opinion solicited as to the participant's appropriateness for inclusion.
6. Willing to allow their GP and/or consultant, if appropriate, to be notified of participation in the study.
7. Willing to provide their national insurance number or passport number to be registered on The Over-Volunteering Prevention System (TOPS).
8. Agree to refrain from blood donation whilst in the study.
9. *For participants of childbearing potential only* (as defined by protocol section 8.3)*:* willing to use effective contraception from one month prior to receiving the first dose of vaccine and for the duration of enrolment in the study (and for a minimum of 18 weeks after final study vaccination) AND have a negative high-sensitivity urine pregnancy test on the days of screening and vaccination.

8.1.2 Exclusion criteria

Participants may not enter the study if any of the following apply:

1. Participation in another research study involving an investigational product, or which includes procedures that could compromise the integrity of this study (such as significant volumes of blood already taken), within the 12 weeks prior to enrollment, or planned participation in such a study within the trial period.

2. History of previous confirmed or suspected CCHF infection.
3. Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
4. Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; severe infection(s); 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 consecutive days within the previous 3 months).
5. History of anaphylaxis in relation to vaccination.
6. 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.
7. History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
8. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
9. History of any serious psychiatric condition likely to affect participation in the study.
10. *For participants of childbearing potential only:* participants who are pregnant, breastfeeding or lactating, or are planning pregnancy during the study.
11. History of a bleeding disorder (*e.g.*, factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
12. 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.
13. History of episodes of capillary leak syndrome.
14. 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 co-morbidities are acceptable)
15. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 14 units per week, or an abnormal GGT
16. Suspected or known injecting drug use within the 5 years preceding enrolment.
17. Detectable circulating hepatitis B surface antigen (HBsAg).
18. Seropositive for hepatitis C virus (antibodies to HCV).
19. Seropositive for HIV.
20. 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.
21. Member of the study team. This is deliberately loosely defined, but at a minimum will include: anyone on the delegation log; anyone who might be anticipated to be placed onto the delegation log in the course of the study; anyone who has access to personal data on study participants (beyond name, contact details, DOB); and anyone who attends meetings where details of the study are discussed, for example safety updates.

8.2 Temporary exclusion criteria

The following apply to both **initial enrolment** and **subsequent vaccination** visits. If the temporary exclusion resolves within the time constraints of the trial, the participant 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. Receipt of systemic antibiotics will result in vaccination being postponed until 7 days after the last antibiotic dose. This does not apply to topical antibiotic preparations.
4. Use of antipyretics in the 4 hours prior to vaccination.
5. Occurrence of a laboratory adverse event, which in the opinion of the Investigator, requires further time and/or investigation to resolve or stabilize prior to a dose of vaccine being administered.
6. Occurrence of any illness or adverse event, which in the opinion of the investigator, requires of further time and/or investigation to resolve prior to a dose of vaccine being administered.
7. Receipt of any vaccines administered within 30 days of study vaccines (before or after) EXCEPT for influenza and COVID-19 vaccines*, which must not be given within 14 days of the study vaccines (before or after).

   * Note that this does not apply to the ChAdOx1-vectored COVID-19 vaccine. Receipt of this vaccine whilst enrolled in the study would result in the participant being withdrawn from the study.

8. Immunisation with a ChAdOx1- or ChAdOx2-vectored vaccine less than 6 months before the first study vaccination visit.
9. Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer if included in the study, affect the ability of the volunteer to participate in the study, or impair interpretation of the study data.

8.3 Pregnancy and contraception

The viral vector component of the ChAdOx2 CCHF vaccine lacks the E1 gene region necessary for replication *in vivo*. No safety signal related to pregnancy has been observed with ChAdOx1 nCov-19 vaccine. The risk of human teratogenicity/fetotoxicity with ChAdOx2 CCHF is therefore considered to be low.

However, the possible adverse effects of the ChAdOx2 CCHF vaccine on the outcome of pregnancy are unknown; therefore, pregnant and breastfeeding/lactating women will be excluded from the study. Should a participant become pregnant during the trial, with their ongoing consent, they will be followed up for clinical safety assessment until the pregnancy outcome is determined. The baby will be followed up for up to 3 months post-delivery. Venepuncture and blood sampling will not be performed in a pregnant volunteer unless there is clinical need.

Participants of childbearing potential will be required to use an effective form of contraception. A participant is considered of childbearing potential (*i.e.,* fertile) from the point following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. 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, and effective contraception would need to be used.

Effective contraception should be established prior to receiving the first dose of vaccine, and for the duration of the study. Acceptable forms of effective contraception for participants of child-bearing potential include:

- Established use of oral, injected or implanted hormonal methods of contraception that inhibit ovulation
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised male partner
- Sexual abstinence when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (*e.g.*, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal methods are NOT acceptable methods of contraception.

Barrier methods of contraception are **not** considered highly effective.

Male participants with female partners are not required to use barrier methods for the purposes of contraception, as the risks of vaccine excretion at mucosal surfaces and in semen are negligible.

9 TRIAL PROCEDURES

9.1 Recruitment

Advertisements for recruitment will be distributed through methods, including, but not limited to, posters, leaflets, websites, newspapers, radio, and/or social media, using advertising material containing wording from REC approved study documents in the first instance to invite participation in the study. Potential participants may be contacted by methods including, but not limited to, email, SMS messaging, telephone, and/or mail, using a REC approved invitation letter.

Where mail-outs are used, participants may be identified via the electoral open register, or through National Health Service databases. 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 our behalf by an external company, CFH Docmail Ltd (or equivalent company), 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 (which 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 which may be used are outline below:

- **Email campaign**: We will contact representatives of local tertiary education establishments and local employers and ask them to circulate posters or advertising material with a link to the study website by email or hard copy.
- **Oxford Vaccine Centre (OVC) database for healthy volunteers**: Direct email and link to members of the public who have registered their interest in potentially volunteering for clinical trials conducted by OVC. This secure database is maintained by OVC, and members of the public registered here have given consent to have their details recorded and to be contacted expressly for the purpose of being notified when a trial opens for recruitment. They understand this is not a commitment to participating in any trial they are contacted about.
- **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.
- **Website advertising**: Description of the study and copy of the information booklet on study team websites.
- **Social media**: Advertisements placed on trial site social media accounts or targeted social media platform advertisements including, but not restricted to, Twitter, Facebook and Instagram.
- **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.
- **SMS/text messages**: SMS/text message (or emails) to potential participants identified by GPs from their databases (which will require Participant Identification Centre [PIC] agreements to be set up with the GP surgeries).
- **Royal Mail Leaflet**: Royal Mail door-to-door service with delivery of invitation letters enclosed 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.

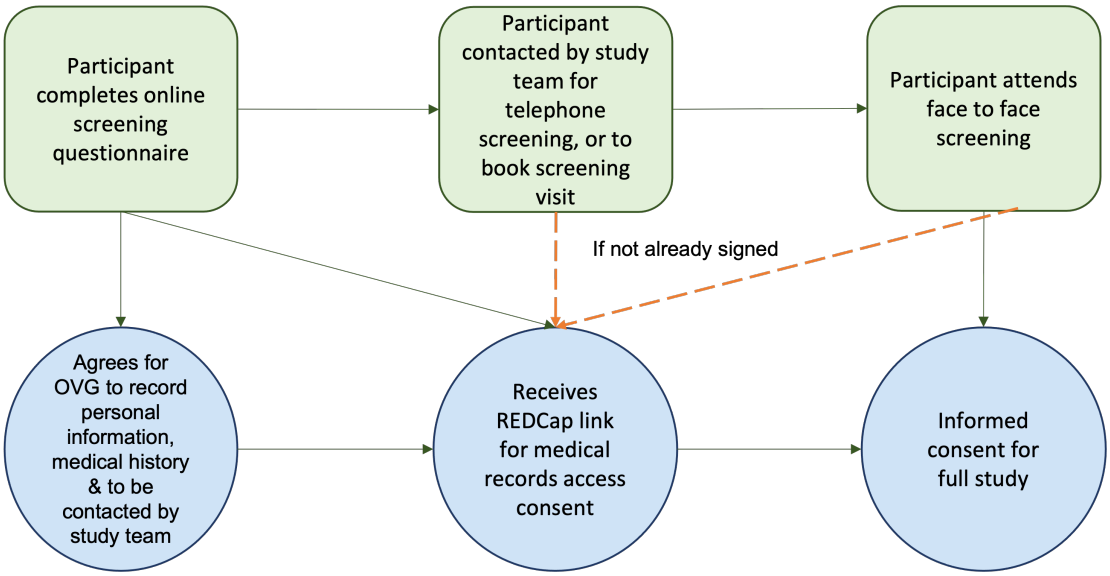
9.2 Screening and eligibility assessment

9.2.1 Initial eligibility assessment of potential study participants

Once an expression of interest has been received, an information sheet will be downloaded from the study website by the potential participant, and/or sent to them via mail or email. Following this information, if participants are willing to proceed, they will be asked to complete an initial online questionnaire, which will include eligibility screening, consent for their personal information and medical history to be recorded by the site, e-consent to access medical and vaccination records. This will be followed by a telephone conversation before they are invited for a full screening and consent visit, where their eligibility will be assessed by a member of the clinical research team. Consent to access the individual's medical and vaccination records, either via the electronic records system or GP, will be sought (if possible) prior to the full screening visit. This will be through signing a secure electronic document (hosted by the REDCap database) which will then be counter-signed by a study

team member. Alternatively electronic consent to access medical and vaccination records will be sought at the individual's full screening and consent visit. A copy of this consent will be provided at the screening visit or posted to the participant if screening visit does not occur

Figure 9: Screening and consent flow



9.2.2 Baseline assessments at screening visit

Once informed written consent has been obtained, the following baseline assessments will be performed and recorded as part of the assessment of inclusion/exclusion criteria:

- Participant demographics: age, sex and ethnicity
- Medical history
- Contraception: participants of childbearing potential are asked if they are willing to use effective contraceptive measures one month prior to vaccination and for the duration of their enrolment in the study; if they withdraw from the study, effective contraceptive measures must be continued until at least 18 weeks after receipt of the last study vaccine.
- Use of concomitant medication (including over the counter medications, vitamins, illicit drug use and herbal supplements)
- Recording of resting pulse, blood pressure, temperature, weight and height
- Physical examination: cardiovascular, respiratory, abdominal and gross neurological examination
- High-sensitivity urine pregnancy test (participants of childbearing potential only)
- Blood samples for full blood count, urea and electrolytes/renal function and liver function tests and random blood glucose
- If the participant has consented to the stool collection component of the study (for cohort 2 only), the procedure for stool collection will be explained and equipment provided for future use.

The medical, vaccination, and prescribed medication history are initially based on participant recall. However, with prior participant consent, 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 an individual's participation in the study.

To avoid unnecessary additional procedures, if the appropriate screening test results are available for the same volunteer from a screening visit for another study at the same trial site that they were not enrolled into, these results may be used for assessing eligibility (provided the results are dated less than 3 months before enrolment in this 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 full screening, however formal registration will be done at enrolment.

9.2.4 Screening failures

Participants who have signed the informed consent form but are not subsequently enrolled in the trial will be regarded as screening failures. For each of these participants, a minimal set of screening 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

No study specific procedures will be performed until the individual has given informed consent and indicated this by signing and dating the informed consent form. The information sheet will be made available to the volunteer at least 24 hours prior to the full screening visit. At the full screening visit, the individual will be fully informed of all aspects of the trial, its potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary.
- Refusal to participate involves no penalty or loss of medical benefits.
- The volunteer may withdraw from the study at any time.
- The individual is free to ask questions at any time to allow them to understand the purpose of the study and the procedures involved.
- The study involves research into an investigational vaccine.
- There is no direct benefit to individuals from participating.
- The volunteer's GP will be informed of their participation in the study.
- Confirmation of their medical history will be required, *e.g.* through a medical history summary from their GP practice or equivalent.
- 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 pseudo-anonymised.

- 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 (OVC Biobank HRA South Central – Hampshire B Research Ethics Committee, 21/SC/0161) which will be consented to separately.

The individual will have the opportunity to discuss the study with a medically qualified investigator. Written informed consent will be given 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

This study does not involve randomisation.

9.5 Study visits

The procedures to be included in each visit are documented in the schedule of procedures tables (Section 0). 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, for both Cohort 1 and Cohort 2, will be as follows:

- Ensure that participant consent remains valid and confirm continued consent
- Obtain and document interim medical history since the screening visit and check eligibility criteria, specifically temporary exclusion to vaccination, and perform a targeted physical examination (if required to reassess eligibility)
- Record temperature, pulse and blood pressure
- Perform high-sensitivity urine pregnancy test for participants of child-bearing potential (section 8.4)
- On the first vaccination visit (D0), provide participant with access and training to use the electronic diary (eDiary) (on REDCap with link sent via email)
- Ensure participant provided with thermometer and tape measure
- On the first vaccination visit (D0), for Cohort 2 only, optional collection of stool sample and supply 'By Post' stool collection kit, as required if participant has consented to this procedure
- Perform blood draw
- Administer vaccine by IM injection into non-dominant deltoid muscle
- Observe volunteer for up to 60 minutes following vaccine administration for Cohort 1. For cohort 2 observation will be for a minimum of 30 minutes provided no concerns observed in cohort 1.
- Schedule next visit and remind participants of what is required of them (*e.g.*, eDiary entries)
- On subsequent vaccination visits, review any AEs, AESIs and SAEs since the last visit

9.5.2 Follow-up visits

Vaccination visits are held at the study site (or remotely, if required, see section 9.5.4). Follow-up visits may require the following procedures:

- Review of AEs/AESIs/SAEs, as appropriate, since the last visit
- Review eDiary entries and laboratory blood tests
- Record oral temperature, pulse and blood pressure
- Perform blood draw
- For cohort 2 only, optional collection of stool sample and supply 'By Post' stool collection kit, as required
- Schedule next visit and re-iterate participant requirements such as eDiary entries
- A high-sensitivity urine pregnancy test will be performed at the final visit for all participants of childbearing potential.

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.

9.6 Electronic diary (eDiary)

Following each vaccination, participants will have access to an electronic diary system (eDiary) 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 and set up using their personal e-mail address. Training for this will be given at the first vaccination visit. 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. Local site clinical teams will have access to the eDiary, in order to review data inputted by participants, and the system automatically sends an email to investigators if a grade 3 AE has been inputted by a participant. The study team will be following up on compliance and will contact participants via phone, text or email to remind participants to fill in the eDiary if this is not being done. The electronic system also automatically sends a reminder to the participant if the eDiary hasn't been completed for the previous 24-hour period.

9.7 Participant samples

9.7.1 Clinical Laboratory samples

Blood will be drawn (at different time points according to the schedule of procedures, section 0) for the following laboratory tests. The processing and analysis of the blood will be carried out at an accredited 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, GGT)
    - Random blood glucose (Screening visit only)
- Diagnostic serology (screening only):
    - Screening tests for Hepatitis B, Hepatitis C and HIV infection (including: HBsAg, HCV antibodies, standard clinical HIV test in a laboratory for example 4th generation HIV antigen/antibody test HIV antibodies)
- Immunology (first vaccination visit only):
    - Human Leukocyte Antigen (HLA) typing

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigator(s).

9.7.2 Immunology samples

9.7.2.1 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.

9.7.2.2 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 peripheral blood mononuclear cells (PBMCs) to these laboratories, but these samples would remain pseudo-anonymised. Informed consent for this will be gained from the volunteers. Immunological assays will be conducted according to local SOPs.

9.7.3 Urine samples

For participants of childbearing potential only, urine will be tested for human chorionic gonadotrophin (hCG) at screening, immediately prior to each vaccination and at the final visit, using a high-sensitivity urine pregnancy test. Alternatively, β-hCG blood sampling may be used to confirm a female participant is not pregnant.

9.7.4 Stool samples

For Cohort 2 only, 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 instructions and equipment provided by the trial team. Sample return instructions will be provided to participants.

9.7.5 Retention of samples

Participants will be informed that they may opt-in to the Oxford Vaccine Centre Biobank study (REC 16/SC/014) to allow long-term storage of biological samples collected under this 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 their remaining samples will be destroyed after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

9.8 Discontinuation/withdrawal of volunteers

Each participant can exercise their right to withdraw from the study at any time without giving a reason. In addition to consent being withdrawn by a participant, the investigator may discontinue a participant from the study at any time for the following, although not exhaustive, reasons:

- The investigator considers it necessary for participant safety
- Significant non-compliance with study requirements
- The participant is lost to follow up

In circumstances pertaining to the safety of the participant, the DSMC chair, DSMC committee or Investigator may choose to discontinue further vaccination and/or study procedures for an individual participant; however, with ongoing consent, monitoring for safety will be continued, *via* either scheduled or unscheduled visits. For example, such circumstances may include the following:

- Pregnancy
- An adverse event which requires discontinuation of the study vaccinations or results in an inability to continue to comply with study procedures
- Ineligibility (either arising during the study or in the form of new information not declared or detected at screening)

Participants of child-bearing potential who withdraw from the study must continue effective contraception until at least 18 weeks after receipt of their last study vaccine.

Withdrawal from the study will not result in exclusion from analysis of existing data generated by the participant. The reason for withdrawal, if given, will be recorded in the CRF.

9.9 Participants invited for COVID-19 vaccination

If the participant receives a ChAdOx-vectored COVID-19 vaccine (*i.e* that manufactured by AstraZeneca) whilst enrolled in the study, they will no longer be eligible to continue in the trial.

10 INVESTIGATIONAL PRODUCT

All participants will receive the interventions scheduled for their allocated cohort/group, as detailed in section 0. The term 'investigational product' applies to ChAdOx2 CCHF.

10.1 ChAdOx2 CCHF

ChAdOx2 CCHF 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 site. The vaccine is supplied as a liquid in single use closed plastic Aseptic Technologies vials (consisting of Cycle Olefin Copolymer vial body, Thermo Plastic Elastomer stopper and Acrylonitrile Butadiene Styrene top and bottom ring, with a nominal volume of 2 ml) for intramuscular administration and will be stored at nominal -80°C in a secure freezer at the clinical site.

Batch number xxx (used for this trial) is presented in A438 formulation buffer: 10mM Histidine, 7 .5% sucrose (w/v), 35mM NaCl, 1mM MgCl2, 0.1% PS80 (w/v), 0.1mM Edetate Disodium, 0.5% ethanol (v/v), pH 6.6. The appearance of ChAdOx2 CCHF is frozen liquid. Once thawed out it presents as a slightly opaque liquid, essentially free from visible particulates.

The dose of ChAdOx2 CCHF to be used in trial will be 5 x 10^{10} virus particles per administration.

10.2 Blinding of IMP

This study is open-label and blinding will not be required.

10.3 Storage of ChAdOx2 CCHF

The drug product ChAdOx2 CCHF is stored according to GMP at -70 to -85 °C at the CBF, University Oxford, UK. Upon QP certification to trial and associated labelling, the vaccine is transferred to each clinical site.

The vaccine is supplied as a liquid in plastic vials for intramuscular administration and is stored at nominal -80°C in a secure freezer at the clinical sites. The freezers are temperature monitored and if outside normal range appropriate action is taken in accordance with previously agreed standard operation procedures (SOPs). A vaccine accountability log will be used to record when the vaccine is removed and used. Vaccine accountability, storage and shipment will be in accordance with the relevant SOP and forms.

On vaccination days, ChAdOx2 CCHF will be allowed to thaw to room temperature and administered within 1 hour. Handling of the vaccine and vaccination will be carried out according to the relevant SOPs. The vaccine will be administered intramuscularly into the deltoid muscle of the non-dominant arm (preferentially) using a suitable sterile needle and syringe.

Throughout the study, the study vaccine will be stored 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 who can move the product in the event of significant temperature deviation.

10.4 Compliance with trial treatment

The study investigational product will be administered by trained 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.

10.5 Accountability of the trial treatment

The ChAdOx2 CCHF 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' and no less than the following:

- The clinical trial identifier (by reference code)
- The content of each vial
- Batch and serial number
- Expiry date
- Chief Investigator's name

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

10.6 Concomitant medication

The use of concomitant medication will be prohibited with the exception of the following: antihistamines, antidepressants, thyroxine, non-opioid analgesics, topical creams including steroid creams that do not significantly alter global immune function, contraceptives. Where other medications are in use, these will be considered on a case-by-case basis by the treating investigator, e.g. the use of some prescribed medicines, such as immune suppressive agents, may result in the withdrawal of the participant at the discretion of the Investigator, while others, such as antibiotics, may result in a temporary exclusion.

New medications that are started throughout the study will not necessarily result in withdrawal and will be considered on a case-by-case basis.

The use of all concomitant medication (prescribed or "over the counter") will be recorded in the CRF.

10.7 Emergency medication and procedures

All clinical staff are trained in the acute management of anaphylaxis reactions, including the use of intra-muscular adrenaline according to site specific SOPs and adrenaline is available at all times of vaccine administration and subsequent observation.

10.8 Post-trial treatment

Study medication will not be continued beyond the trial period.

10.9 Other treatments (non-IMPs)

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

10.10 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 hospitalization or prolongation of existing hospitalization, • Results in persistent or significant disability/incapacity, or • 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	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:

Adverse Reaction (SUSAR)	• In the case of a product with a marketing authorization, in the approved summary of product characteristics (SmPC) for that product, or • In the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.
Adverse Events of Special Interest (AESI)	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an event might require further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

NOTE: 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 6). Additionally, other adverse events (*i.e.*, not listed below) may also be categorised by investigators as AESIs if scientifically warranted.

There is no previous clinical experience with ChAdOx2 CCHF. There is extensive clinical experience of ChAdOx1 nCoV-19 vaccine (AZD1222), marketed as Vaxzevria in the UK, a vaccine based on a similar vaccine platform technology. Adverse reactions based on five clinical trials and post authorisation experience are tabulated in Table 7 below.

Given that it is not known whether there will be any similarity in clinical safety profile between ChAdOx2 CCHF and ChAdOx1 nCoV-19 vaccine (AZD1222), monitoring of adverse events of special interest will include adverse reactions listed in the summary of product characteristics for Vaxzevria that are considered clinically significant.[53]

Investigators managing a case of suspected vaccine-induced immune thrombocytopenia and thrombosis (VITT), also known as Thrombosis with Thrombocytopenia Syndrome (TTS), should refer to the NICE guidance on diagnosis and treatment.[64]

Table 7 List of Adverse Events of Special Interest (AESIs)

Respiratory	Acute Respiratory Distress Syndrome (ARDS)
	Pneumonitis
Neurological	Transverse Myelitis
	Generalised convulsion
	Guillain-Barre Syndrome (GBS)
	Acute Disseminated Encephalomyelitis (AE)
	Encephalopathy
	Encephalitis
	Stroke
	Facial paralysis
Haematological / Vascular	Thrombocytopenia
	Thrombosis with Thrombocytopenia Syndrome (TTS)
	Major thrombosis (without thrombocytopenia)
	Heparin-Induced Thrombocytopenia
	Immune thrombocytopenic purpura
	Disseminated intravascular coagulation (DIC)
Immunological	Anaphylaxis
	Angioedema
	Urticaria
	Vasculitis
	Capillary Leak Syndrome (CLS)
	Other Immune-mediated conditions
Other	Acute renal failure
	Muscle spasms

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

Table 8 Adverse reactions to ChAdOx1 *nCoV-19* vaccine (AZD1222)

MedDRA SOC	Term	Frequency*	Monitored AESI**
Blood and lymphatic system disorders	Lymphadenopathy	Uncommon	No
	Thrombocytopenia, Immune thrombocytopenia	Uncommon	Yes
Immune system disorders	Anaphylaxis, hypersensitivity	Uncommon	Yes
Metabolism and nutrition disorders	Decreased appetite	Uncommon	No
Nervous system disorders	Headache	Very common	No
	Dizziness, somnolence, lethargy	Uncommon	No
	Facial paralysis	Rare	Yes
	Guillain-Barré syndrome	Very rare	Yes
	Transverse myelitis	Not known	Yes
Vascular disorders	Thrombosis with thrombocytopenia syndrome	Very rare	Yes
	Cerebrovascular venous and sinus thrombosis	Not known	Yes
	Capillary leak syndrome	Not known	Yes
Gastrointestinal disorders	Nausea	Very common	No
	Vomiting, diarrhoea	Common	No
	Abdominal pain	Uncommon	No
Skin and subcutaneous tissue disorders	Hyperhidrosis, pruritus, rash, urticaria	Uncommon	Yes (urticaria)
	Angioedema	Not known	Yes
Musculoskeletal and connective tissue disorders	Myalgia, arthralgia	Very common	No
	Pain in extremity	Common	No
	Muscle spasms	Uncommon	Yes
General disorders and administration site conditions	Injection site tenderness, pain, warmth, pruritus, bruising, fatigue, malaise, feverishness, chills	Very common	No
	Injection site swelling, erythema, induration, pyrexia, influenza-like illness, asthenia	Common	No

* very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated)

**AEs listed that are not AESIs will be captured as solicited and/or unsolicited AEs

11.3 Causality assessment

The relationship of each adverse event to the trial vaccine or study procedures must be determined by a PI-delegated 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 8):

Table 8 Guidelines for assessing the relationship of vaccine administration to an Adverse Event

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

All serious adverse reactions (serious adverse events assessed as possible, probable or definitely related to ChAdOx2CCHF administration) will be assessed for expectedness by the investigator. Expectedness will be determined according to the information set out in the reference safety section of the ChAdOx2 CCHF IB. As no expected SARs are recorded in the reference safety section of the ChAdOx2 CCHF IB, any SARs associated with ChAdOx2 CCHF 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 volunteers enrolled in preventive vaccine clinical trials. Severity scales for clinical and laboratory adverse events are shown in Appendix E.

11.6 Procedures for collecting and recording Adverse Events

Abnormal clinical findings from medical history, examination or blood tests will be assessed by a delegated clinician / Investigator to determine clinical significance.

All AEs that are observed by the Investigator or reported by the participant, irrespective of their relatedness to the study vaccination, will be recorded from the day of vaccination and until 28 days after each vaccination. These will be either recorded by the participants in the e-diary and/or in the 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 by the study team.

Table 9: Recording of solicited and unsolicited adverse events

Type of AE	Study period	eDiary	eCRF
Solicited	Day 0-7	X	
Unsolicited	Day 0-7	X	X
	Day 8-28 post each vaccine dose	X	X
	Day 28-end of study (medically attended AEs only)		X

11.7 Solicited Adverse Events

Predefined local and systemic solicited AEs for reactogenicity assessment, as listed in Table 9, will be collected in an electronic diary for 7 days following administration of the vaccine (see table x). Participants will measure and record their temperature and the diameter of any injection site redness or swelling with a 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 in the diary. Any solicited AE which meets the definition of a SAE will be managed and reported as per Section 11.5.

Table 10 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

11.8 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 from the day IMP is administered to the end of the study as follows:

- Day 0 – day 28 post each vaccine: These will be recorded in the participant's eDiary and/or ecRF. All reported events will be reviewed at clinic visits and transferred to relevant eCRF on the clinical database if necessary.
- Day 28 to subsequent vaccination or until the final visit (if vaccination course completed) only non-serious medically attended AEs that occur from the time of vaccination to the end of the study will be recorded in the relevant eCRF on the clinical database.

Severity will be self-assessed by participants according to severity grading scales provided to them. Causality will be assigned by the PI-delegated clinician / Investigator as per section 11.3.

If clarification of any event is required, then the study nurse or doctor will seek this from the participant during a clinic visit or by telephone call.

11.9 Observation related AEs

Physical observations of the patient (*e.g.,* temperature, blood pressure) will be taken at each visit. These will be recorded in the eCRF. If abnormal, a severity grading will be assigned as described in Appendix E.

11.10 Laboratory AEs

Severity grading for laboratory AEs is described in Appendix E. All changes in laboratory values will be recorded as AEs if they are of Grade 2 severity or above and will be entered into the relevant eCRF in the clinical database. Changes of laboratory values of Grade 1 severity may be recorded as AEs if they are judged to be clinically significant by a PI-delegated clinician / Investigator.

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

A Grade 4 laboratory AE will be considered a SAE.

11.11 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 will be recorded to represent a single diagnosis. Accompanying signs or symptoms (including abnormal laboratory values) will 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, in which case 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 the ongoing consent of the participant.

11.12 Follow up of AEs

AEs considered related to the active vaccine 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 PI-delegated clinician / Investigator, to ensure, if not already done so, that adequate medical follow-up (if required) has been arranged, *e.g.* referral to the participant's GP.

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.

11.13 Reporting procedures for SAEs

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

All SAEs must be recorded on a SAE form (on REDCap, or paper backup) with causality assessed by the Investigator and reported by email to the CI. All SAEs will be reported to the DSMC Chair (or nominated designee) within 24 hours of discovery or notification of the event. If the PI deems that this is a SUSAR, this will be reported according to the SUSAR reporting procedures in section 11.14. In the absence of the PI these tasks may be performed by a Co-Investigator.

Additional information received for a case (follow-up or corrections to the original case) will be detailed on an electronic SAE form which is linked to the original report. An automated email alert will be sent to the CI, the lead study Dr, the Quality Assurance lead, the lead nurse, the project manager and the sponsor assessors.

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 safety assessment throughout the study as per section 11.18.

11.14 SUSAR reporting

All SUSARs will be reported to the Sponsor, DSMC, 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 8 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.

11.15 Development Safety Update Report

The CTU (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 ChAdOx2 CCHF is the date of approval from the MHRA and the data lock point of each DSUR will be the last day of each one-year reporting period.

11.16 Safety profile review

The safety profile will undergo review on a day-to-day basis by the Investigators using the electronic diary, adverse events CRF and safety bloods. Any concerns will be referred to the CI. Interim safety reviews will be carried out in Oxford by the CI and at external sites by the CI and local PI via email and/or telephone. If the CI remains concerned, they may consider escalation to the DSMC as required.

11.17 Trial Management Group

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

11.18 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.

11.19 Interim safety reviews

11.19.1 Sequence of enrolment and study vaccination

Enrolment of Cohort 1: An initial cohort of six participants will be enrolled and receive their first study vaccine prior to the enrolment of further participants. Enrolment will be staggered (Table 10).

Sentinel participant: The first participant enrolled into the trial will be vaccinated alone, ahead of any other participants. Their profile of adverse events will be reviewed for 2 days post-vaccination.

Participants 2 and 3: Provided there are no safety concerns, as assessed by the CI a further two participants will be vaccinated.

Participants 4, 5 and 6: The accumulated profile of adverse events for first, second and third participants will be reviewed by the CI after two days and if deemed acceptable, the remaining three participants in Cohort 1 will be vaccinated.

Enrolment and study vaccination of Cohort 2: This will occur after a positive decision from the DSMC following the first DSMC safety review (detailed below in section 11.19.3).

Table 11 Sequence of Enrolment for First Doses

Sequence	**Participant groups**	**Minimum interval before next step**	**Safety review before progression**
Step 1	Cohort 1 volunteer 1	2 days	Local safety review by CI
Step 2	Cohort 1 volunteers 2 and 3	2 days	Local safety review by CI of Cohort 1 volunteers 1, 2 and 3
Step 3	Cohort 1 remaining volunteers	7 days	DSMC review
Step 4	Cohort 2	n/a	n/a
Step 5	6 participants who have a 2nd dose from either cohort	7 days	Safety review by CI & site PI where appropriate

11.19.2 Sequence of second study vaccine doses

Second study vaccination of Cohort 1 and 2 will be staggered. A second dose of study vaccine will be given to six enrolled participants. The CI and (and where appropriate), PI will conduct a formal safety review of the accumulated safety data from Day 0 to Day 7 following the second study vaccination. This safety dataset will comprise 6 participants who have a 2nd dose from either cohort. If there are no safety concerns, the remaining participants will receive their second dose of study vaccine.

11.19.3 DSMC safety reviews

DSMC data review will be done as follows:

1. Formal review of the safety profile data after 7 days (Day 0 to Day 7 inclusive) following the first vaccination of all six participants in Cohort 1. This review will decide on progression to enrolling and administering the first dose of vaccine to the remaining participants in the trial *(i.e*. Cohort 2). The review will also decide on progression to administering the second dose of study vaccine to all participants .

2. Formal review of the safety profile, including safety data up to a minimum of 28 days after the second dose of vaccine has been administered to all participants.
3. Independent review following any SAE deemed to be related to the trial active vaccine.
4. 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 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.

11.20 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 for clinical significance throughout the trial. If a test is deemed clinically significant, it may be repeated to ensure it is not a single occurrence or spurious result. If a test remains clinically significant, the participant will be informed, and appropriate medical care arranged as appropriate, with the permission of the participant. Decisions to exclude the participant from enrolling in the trial or to withdraw a participant from the trial will be at the discretion of the Investigator.

11.21 Safety holding rules

11.21.1 Group holding rules

If two or more of the participants in either cohort develop the same unacceptable adverse reaction then study vaccination will be paused pending a DSMC review.

An unacceptable adverse reaction is an adverse event (solicited or unsolicited) occurring within two days after a dose of study vaccination that is severe, with severity lasting at Grade 3 or more for more than 48 hours, and in the opinion of the Chief Investigator and in the opinion of the treating investigator is considered possibly, probably or definitely related to the study vaccination .The treating investigator's assessment of relatedness will not be downgraded by another member of the research study team. Adverse events occurring after study vaccination that meet these criteria but have a plausible alternative causality will not trigger the holding rule.

- **Solicited local Adverse Events**:
    - if ≥2 participants in either cohort experience the same Grade 3 solicited local adverse event beginning within 2 days after vaccination (day of vaccination D0 and one subsequent day D1) and persisting at Grade 3 for >48 hrs.
- **Solicited systemic Adverse Events**:
    - if ≥2 participants in either cohort experience the same Grade 3 solicited systemic adverse event beginning within 2 days after vaccination (on the day of vaccination [D0 or V2] or on the subsequent day [D1 or V2+1]) and persisting at Grade 3 for >48 hrs.
- **Unsolicited Adverse Events**:

- if ≥2 participants in either cohort 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.
- A serious adverse event considered possibly, probably or definitely related to vaccination occurs.
- Death occurs.
- A life-threatening reaction occurs.

If a holding rule has been met and following a safety review by the DSMC it is deemed appropriate to restart dosing. A resumption of dosing can only take place after the regulatory authority approves a substantial amendment application in which with pertinent data is presented.

The DSMC safety review will 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.
- New, relevant safety information from ongoing research programs on the various components of the vaccine.

The DSMC will not downgrade the assessment of an investigator from related to unrelated.

The local ethics committee, MHRA and vaccine manufacturers will also be notified if a holding rule is activated or released.

All vaccinated participants 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.

11.21.2 Individual holding rules

In addition to the above stated group holding rule, stopping rules for individual participants will apply (*i.e.,* indications to withdraw individuals from further vaccinations) where the event is considered clinically significant by the investigator:

- **Local reactions**: the participant develops injection site ulceration, abscess or necrosis.
- **Systemic solicited adverse events**: the participant develops a Grade 3 systemic solicited adverse event considered possibly, probably, or definitely related to vaccination within 2 days after vaccination (on the day of vaccination [D0 or V2] or on the subsequent day [D1 or V2+1]) and persisting at Grade 3 for >48hrs.
- **Laboratory AEs**: the participant 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 > 7 days (laboratory AE reference ranges are shown in Appendix E).
- **Unsolicited adverse events**:
  - The participant has a Grade 3 adverse event considered possibly, probably, or definitely related to vaccination, persisting at Grade 3 for >48hrs.

- The participant has a serious adverse event considered possibly, probably or definitely related to vaccination.
- The participant has an acute allergic reaction or anaphylactic shock following the administration of an investigational product.

If a participant fulfils any of the temporary exclusion criteria at the scheduled time of a second administration of investigational product, the participant 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 participants 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.

11.22 Criteria for termination of the trial

The CI and DSMC 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.

In the event of the trial being terminated early, follow-up of enrolled participants will continue as planned for safety reasons, but further vaccination will not be given, and study procedures will be modified to monitor safety only.

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 the participants' CRFs, which will be in a paper and/or electronic format using an EDC system (e.g. REDCap database, or an appropriate alternative). The database will be stored on a secure server located in Europe and will have restricted access (password-protection) and accountability records. All information transcribed to and from the REDCap database will be done by encrypted (https) transfer.

Each study participant will have a unique participant number which will be allocated at the time of the screening visit. 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. Participants will be identified by a study-specific participant number and/or code, which will be allocated at the screening visit. 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.

12.1 Data integrity

Data collection and storage will be inspected throughout the study by internal monitors appointed by the Oxford Vaccine Group on behalf of the study Sponsor, University of Oxford Research Governance, Ethics and Assurance (RGEA).

12.2 Data archiving and storage

Study data may be stored electronically on a secure server operated by the University IT team, and paper notes will be kept in a key-locked filing cabinet at the study site. All essential documents will be retained for a minimum of 5 years after the study has finished. Volunteers who only complete online screening or telephone screening (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 for a minimum of 7 years in line with the site financial policy. Pseudo-anonymised 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 or GP 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 (or appointed by) 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 the EDC system if direct entry is not available. Any additional information that needs recording but is not relevant for the CRF (such as signed consent forms) 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 personnel. The servers are in a physically secure location in Europe, and data are backed up on secure servers operated by the University of Oxford IT Services, physically located in Europe. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. Weekly backup tapes are stored offsite. The servers provide a stable, secure, well-maintained, and high-capacity data storage environment. REDCap is a widely used, powerful, reliable, well-supported system. Access to the study's database will be restricted to the members of the study team by username and password.

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 in 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, power calculation, or presentation of p-values for group comparisons.

13.1.2 The number of participants

Forty-six participants will be recruited to the study and allocated to cohorts 1 or 2. Participants will be replaced only if they do not receive the first dose of vaccine. The number of participants has been chosen pragmatically, to 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 reported as 95% confidence intervals.

13.1.4 Procedure for accounting for missing, unused, and spurious data

All available data will be used in the analyses and there will be no imputation for missing data.

13.1.5 Inclusion in analysis

All participants with any available data will be included in the analyses. Participants will be analysed according to the group to which they were assigned.

13.1.6 Interim analysis

Interim analyses of safety outcomes will occur at the interim safety reviews as described in Section 11.19.3.

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), MHRA, regulatory authorities, and host institutions 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 within 12 months of the end of trial (as declared 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

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

14.6 Participant confidentiality

The trial staff will ensure that the participants' anonymity is maintained. 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

Volunteers will be compensated £110 for attending the screening visit and vaccination visits, £90 for each of the trial follow-up visits, and £30 for completion of each diary card. Additional reimbursement for unscheduled visits at £90 per visit will be provided. This will not be given unless an unscheduled visit occurs. The total amount of compensation for an individual participant will depend on the actual number of visits attended and whether any repeat or additional visits were necessary. If a participant withdraws consent for continued participation in the trial or is withdrawn for any other reason, they will still be compensated for any trial visits they attended. Each participant can therefore receive a maximum of £1,470 (Cohort 1) and £1,110 (Cohort 2) for the study visits plus an additional amount, based on whether unscheduled visits were required and how many occurred.

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 the RGEA or parties appointed by the Sponsor. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported, in compliance with the protocol, GCP and the applicable regulatory requirements. The Investigator site 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 and inspection

The Quality Assurance manager operates an internal audit program to ensure that the systems used to conduct clinical research are present, functional, and enable research to be conducted in accordance with study protocols and regulatory requirements. Audits include laboratory activities covering sample receipt, processing and storage and assay validation. The internal audits will

supplement the external monitoring process and will review processes not covered by the external monitor.

The Sponsor, 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.

15.6 Communication plan

Important study information will be communicated to Oxford and site study teams via weekly, minuted study meetings and circulated to the Oxford and site study teams as applicable. All documents will be available in the TMF/ISF, on the shared network drive for the Oxford team and via a secure portal e.g. SharePoint for the site teams. Weekly meetings will be either in person or via a virtual platform e.g. Teams or Zoom or where feasible in person.

For the interim safety reviews described in sections 11.19-11.20 the following process will apply:

- The study statistician will provide a complete data set for review.
- CI (or designated individual) reviews the safety data with lead fellow (or designated individual), and/or site PI (or designated individual) where applicable
- An interim safety review report will be generated and signed by the CI (or designated individual), the lead fellow (or designated individual) and/or site PI (or designated individual) where applicable.
- The report is communicated to the Oxford and site study teams (where applicable) by email and the email confirms to the study team if the next participant can be vaccinated.
- The report and email will be filed as PDFS in TMF/ISF.
- Interim safety review reports will be signed, dated, and time of signing documented.
- For DSMC reviews the DSMC letter or email confirming the study can continue will be shared with the CI, site PI and Oxford and site study teams (where applicable)
- Communication will be via email and/or phone. For the Oxford site this could also be in person. All phone or in person discussions will be confirmed via email.

All important communication will be filed as PDFs in the TMF/ISF

16 FINANCING AND INSURANCE

16.1 Financing

The study is funded by UK Research and Innovation.

16.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm resulting from 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".

If 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.

A lay summary of the study results may be provided to participants at the end of the study.

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	
AE	Adverse event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Adverse reaction
AST	Aspartate aminotransferase
CBF	Clinical Biomanufacturing Facility
CCHF	Crimean-Congo haemorrhagic fever
CCHFV	Crimean-Congo haemorrhagic fever virus
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
ChAd63	Chimpanzee Adenovirus serotype 63
ChAdOx1	Chimpanzee Adenovirus Ox1
ChAdOx2	Chimpanzee Adenovirus Ox2
CI	Chief Investigator
CLS	Capillary leak syndrome
CMV	Human cytomegalovirus
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CVST	Cerebral venous sinus thrombosis
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Committee
DSUR	Development Safety Update Report
EBV	Epstein Barr virus
EBOV	Zaire Ebolavirus
EDC	Electronic Data Capture
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunosorbent spot assay
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
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
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
IB	Investigators Brochure
ICH	International Conference on Harmonisation
IFN	Interferon
IM	Intramuscular/intramuscularly
IMP	Investigational medicinal product

Abbreviations	
ISF	Investigator Site File
ITP	Immune thrombocytopaenia purpura
IU	Infectious units
IUD	Intrauterine device
IUS	Intrauterine system
JCVI	Joint Committee on Vaccination and Immunisation
LVLV	Last volunteer last visit
MedRA	Medical Dictionary for Regulatory Activities
MERS	Middle Eastern Respiratory Syndrome
MERS-CoV	Middle Eastern Respiratory Syndrome-Related Coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	Messenger ribonucleic acid
MVA	Modified Vaccinia Virus Ankara
NAAT	Nucleic Acid Amplification Test
NCT Number	National Clinical Trial number
NHAIS	National Health Applications and Infrastructure Services
OVC	Oxford vaccine centre
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PFU	Plaque forming units
PIC	Participant Identification Centre
PIS	Participant information sheet
POCBP	Participant of childbearing potential
QP	Qualified Person
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance (formerly Clinical Trials and Research Governance)
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tec_VLP	transcription- and entry-competent virus-like particles
TMF	Trial Master File
TOPS	The Over-Volunteering Prevention System
TTS	Thrombosis with thrombocytopenia syndrome
UKHSA	United Kingdom Health Security Agency
VITT	Vaccine-induced immune thrombotic thrombocytopaenia
vp	Viral particles
WHO	World Health Organization

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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 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:

Chief Investigator	Signature	Date:

Principal Investigator Approval, Agreement and Conflict of Interest statement

Site 1: xxx

I have read the trial protocol 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	Signature	Date:

Site 2: xxx

I have read the trial protocol 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	Signature	Date:

23 Appendix B: Document history

Amendment No.	Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	V1.0		Philip de Whalley	Initial document
1	V2.0	30 June 2023	Sarah Kelly	• Section 8.1.1: - Inclusion criteria No.2 amended to state participant must be in good health as determined by medical history, physical exam and clinical judgement of the investigators • Section 8.1.2: - Exclusion criteria No.15: ▪ Definition of alcohol abuse amended to read '..alcohol intake of greater than 14 units per week' ▪ addition of abnormal GGT result • Section 10.6 - Concomitant medications revised to prohibit all but the following medications antidepressants, thyroxine, non-opioid analgesics, topical creams including steroid creams that do not significantly alter global immune function, contraceptives and to allow for investigator discretion around the use of some prescribed medications e.g. use of antibiotics • Section 11.21.1: - Wording for group & individual holding rules amended - Clarification that the investigators assessment of an AE may not be amended by any team member or the DSMC - Statement about additional testing for volunteers following a DSMC review deleted - Statement about resumption of study after a pause amended to state more clearly that regulatory approval is required • Wording around urine pregnancy tests updates to say high-sensitivity urine pregnancy tests • Additional pregnancy test added to final visit for all participants of child-bearing potential

24 Appendix C: ChAdOx1 and ChAdOx2 vaccines in clinical-phase development

IMP	Indication	First clinical trial application date (approx.)
ChAdOX1 NP+M1	Influenza	01/05/2012
ChAdOx1 85A	Tuberculosis	21/02/2013
ChAdOx1 5T4	Prostate Cancer	24/12/2014
ChAdOx1 LS2	Malaria (liver stage)	27/04/2017
ChAdOx1.HTI	HIV	07/07/2017
ChAdOx1 MenB.1	Meningitis B	23/11/2017
ChAdOx1 MERS	MERS-CoV	24/11/2017
ChAdOx1 CHIK	Chikungunya	26/04/2018
ChAdOx1 ZIKA	Zika	12/04/2019
ChAdOx1-HBV	Hepatitis B	11/11/2019
ChAdOx1 nCoV-19*	COVID-19	18/03/2020
ChAdOx1.tHIVconsv1	HIV	19/03/2020
ChAdOx1 Plague	Plague	29/10/2020
ChAdOx1-HPV	Human papillomavirus infection / CIN1	29/10/2020
ChAdOx1 RVF	Rift valley fever	14/12/2020
ChAdOx1-MAGEA3-NYESO	Non-small-cell lung cancer therapeutic	01/06/2021
ChAdOx1 biEBOV	Zaire & Sudan ebolavirus	25/08/2021
ChAdOx1 NipahB	Nipah	Pending
ChAdOx2 MAP	Paratuberculosis	24/05/2019
ChAdOx2 RabG	Rabies	14/11/2019

*Licensed vaccine

25 Appendix D: Clinical trials of ChAdOx1- and ChAdOx2-vectored vaccines sponsored by the University of Oxford

Vaccine	Trial	Country	Age	Number	Dose ($x10^{10}$vp)	Route	Registration
ChAdOx1 NP+M1 (+MVA-NP+M1)	FLU005	UK	18-50	48	2.5	i.m.	NCT01818362
			50+	24			
ChAdOx1 85A (+MVA85A)	TB034	UK	18-49	6	0.5	i.m	NCT01829490
				12	2.5		
				12	2.5 +MVA85A		
				12	2.5 (x2) +MVA85A		
ChAdOx1.5T4 (+MVA 5T4)	VANCE01	UK	18-75	34	2.5	i.m.	NCT02390063
ChAdOx1.5T4 (+MVA 5T4)	ADVANCE	UK	≥18	23	2.5	i.m.	NCT02815942
ChAdOx1 LS2	VAC067	UK	18-45	3	0.5	i.m.	NCT02302421
				10	2.5		
ChAdOx1 MenB.1	VAMBOX	UK		3	2.5	i.m.	ISRCTN46336916
				26	5		
ChAdOx1 MERS	MERS002	UK	18-50	6	0.5	i.m.	NCT03399578
				9	2.5		
				9	5		
				5	2.5 (x2)		
ChAdOx1 MERS	MERS002	Saudi Arabia	18-50	6	0.5	i.m.	NCT04170829
				9	2.5		
				9	5		

Vaccine	Trial	Country	Age	Number	Dose ($x10^{10}$vp)	Route	Registration
ChAdOx1 Chik	CHIK001	UK	18-50	6	0.5	i.m.	NCT03590392
				9	2.5		
				9	5		
ChAdOx1 Zika	ZIKA001	UK	18-50	6	0.5	i.m.	NCT04015648
				9	2.5		
				9	5		
ChAdOx1 Chik	CHIKA01	Mexico	18-50	12	0.5	i.m.	NCT04440774
ChAdOx1 Zika	CHIKA01	Mexico	18-50	12	0.5	i.m.	NCT04440774
ChAdOx1 Chik & ChAdOx1 Zika	CHIKA01	Mexico	18-50	12	0.5	i.m.	NCT04440774
ChAdOx1 nCoV-19	COV001	UK	18-55	533	5	i.m.	NCT04324606
ChAdOx1 nCoV-19	COV002	UK	18-55	4138	5	i.m.	NCT04400838
			56-69	149			
			≥70	186			
ChAdOx1 nCoV-19	COV003	Brazil	18-55	5209	5	i.m.	ISRCTN89951424
ChAdOx1 nCoV-19	COV004	Kenya		139	5	i.m.	PACTR202005681895696
ChAdOx1 nCoV-19	COV005	South Africa	18-65	1061	5	i.m.	NCT04444674
ChAdOx1 nCoV-19	COV006	UK	5-11	90	5	i.m.	ISRCTN15638344
			12-17	120			
ChAdOx1 nCoV-19	COV008	UK	18-55	6	0.5	Intra-nasal	NCT04816019
				12	2.5		
				24	5		
ChAdOx1 RVF	RVF001	UK	18-50	3	0.5	i.m.	NCT04754776
				6	2.5		
				6	5		

Vaccine	Trial	Country	Age	Number	Dose ($x10^{10}$vp)	Route	Registration
ChAdOx1 RVF	RVF001	Uganda	18-50	4	0.5	i.m.	NCT04672824
				10	2.5		
				10	5		
ChAdOx1.tHIVconsv1	HIV-CORE 0051	UK	18-65	10	5	i.m.	NCT04563377
ChAdOx1.tHIVconsv1	HIV-CORE 0052	UK	18-65	3	0.5	i.m.	NCT04586673
				6	5		
ChAdOx1.tHIVconsv1	HIV-CORE 006	Africa multi-site	18-50	72	5	i.m.	NCT04553016
ChAdOx1 Plague	PlaVac	UK	18-55	45	5	i.m.	ISRCTN 27841311
ChAdOx1 biEBOV	EBL07	UK	18-55	6	0.5	i.m	NCT05079750
				6	2.5		
				7	5		
				7	5 (x2)		
ChAdOx1 biEBOV	EBL08	UK	18-45	7	0.5	i.m.	NCT05301504
				7	2.5		
				28	5		
ChAdOx2 RabG	RAB001	UK	18-65	3	0.5	i.m.	NCT04162600
				3	2.5		
				6	5		

26 Appendix E: Grading the severity of adverse events

1. Solicited and unsolicited adverse events

Adverse event	Grade	Definition (in degrees Celsius)
Temperature	0	< 37.6
	1	37.6 – 38.0
	2	38.1 – 39.0
	3	> 39

Adverse event	Grade	Definition
Any symptom	0	Absence or resolution of symptom
	1	Awareness of symptom but tolerated; transient or mild discomfort; little or no medical intervention required
	2	Discomfort enough to cause limitation of usual activity; some medical intervention or therapy required
	3	Significant interference with daily activity
	4	Emergency department visit or hospitalisation
	5*	Fatality

*All grade 5 AEs will be considered either a SAE, SAR, or SUSAR dependant on causality and 'expectedness'

2. Visit observed adverse events

Observation	Grade 1	Grade 2	Grade 3
Oral temperature (°C)	37.6 – 38.0	38.1 – 39.0	>39
Tachycardia (beats/min)	101-115	116-130	>130
Bradycardia (beats/min)	50-54	45-49	<45
Systolic hypertension (mmHg)	141-150	151-155	>155
Diastolic hypertension (mmHg)	91-95	96-100	>100
Systolic hypotension (mmHg)	85-89	80-84	<80

The following are considered normal physiological ranges and are recorded as Grade 0:

- Oral temperature between 35.5 and 37.5 C
- Resting heart rate between 55 and 100 beats/minute
- Systolic blood pressure between 90 and 140 mmHg

3. Laboratory adverse events

Parameter	Grade 1	Grade 2	Grade 3	Grade 4*
Haemoglobin: decrease from baseline value (g/l)	10 – 15	16-20	21-50	>50
White cell count: elevated (10^9/L)	11–15	16–20	21–25	>25
White cell count: depressed (10^9/L)	2.5-3.5	1.5-2.4	1.0-1.4	<1.0
Neutrophil count (10^9/L)	1.5-2.0	1.0-1.4	0.5-0.9	<0.5
Platelets (10^9/L)	125-140	100-124	25-99	<25
Sodium: hyponatraemia (mmol/L)	132–134	130–131	125–129	<125
Sodium: hypernatraemia (mmol/L)	146	147	148–150	>150
Potassium: hyperkalaemia (mmol/L)	5.1–5.2	5.3–5.4	5.5–5.6	>5.6
Potassium: hypokalaemia (mmol/L)	3.3–3.4	3.1–3.2	3.0	<3.0
Urea (mmol/L)	8.2–8.9	9.0–11	>11	RRT
Creatinine (µmol/L)	132-150	151-176	177-221	>221 or RRT
ALT and/or AST (IU/L)	1.1–2.5 x ULN	>2.6–5.0 x ULN	5.1-10 x ULN	>10 x ULN
Bilirubin, with increase in LFTs (µmol/L)	1.1–1.25 x ULN	1.26–1.5 x ULN	1.51–1.75 x ULN	>1.75 x ULN
Bilirubin, with normal LFTs (µmol/L)	1.1–1.5 x ULN	1.6–2.0 x ULN	2.1–3.0 x ULN	>3.0 x ULN
Alkaline phosphatase (IU/L)	1.1–2.0 x ULN	2.1–3.0 x ULN	3.1–10 x ULN	>10 x ULN
Albumin: hypoalbuminaemia (g/L)	28–31	25–27	<25	Not applicable
C-reactive protein	>10-30	31-100	101-200	>200

*Grade 4 = Potentially life-threatening

ULN: Upper limit of normal (using site laboratory reference range)

RRT: Renal replacement therapy