Full title: A phase I safety and immunogenicity study of a Nipah virus vaccine, ChAdOx1 NipahB, in healthy volunteers aged 18 to 55 in the UK

Short Title: A study of a new vaccine against Nipah Virus in adults aged 18 to 55

Study Code: NIV001

Internal Reference Number: OVG 2023/02

Protocol Version: 4.0

Date: 16 AUG 2024

Chief Investigator: Professor Brian Angus

Lead Scientific Investigator: Professor Dame Sarah Gilbert

Sponsor: University of Oxford

Funder: CEPI

REC Details: South Central - Oxford A Research Ethics Committee

REC Number: 23/SC/0268

EudraCT Number: 2023-503872-25-00

IRAS Project ID: 1007433

ISRCTN Registry Number: 87634044

PAGE LEFT INTENTIONALLY BLANK

Table of Contents

1 KEY TRIAL CONTACTS

Chief Investigator	Professor Brian Angus Professor of Infectious Diseases / Consultant Physician Director Oxford Centre for Clinical Tropical Medicine, University of Oxford Nuffield Department of Medicine Research Building (NDRMB) Old Road Campus, Headington Oxford OX3 7FZ
Lead Scientific Investigator	Professor Dame Sarah Gilbert Old Road Research Campus Building Headington Oxford OX3 7DQ
Principal Investigators / Trial Site(s)	
	Professor Brian Angus Oxford University Hospitals Foundation Trust Headley Way, Headington, Oxford OX3 9DU
Sponsoring Institution	University of Oxford Research Governance, Ethics & Assurance Team (RGEA) Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB Tel: 01865 616480 Email: RGEA.Sponsor@admin.ox.ac.uk
Clinical Trial Monitor	Oxford Vaccine Group (OVG) Internal Quality Assurance team Oxford Vaccine Group Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) Churchill Hospital Oxford OX3 7LE
Statistician	Dr Xinxue Liu and Natalie Marchevsky Oxford Vaccine Group Centre for Clinical Vaccinology and Tropical Medicine (CCVTM) Churchill Hospital Oxford OX3 7LE
DSMC Chair	Dr Martha Nason Biostatistics Research Branch, NIAID, NIH 5601 Fishers Lane Rockville, USA

2 LAY SUMMARY

This is a trial of a new vaccine against Nipah virus. Nipah virus is a potentially fatal infection that can cause severe breathing problems and abnormalities with the nervous system including the brain. It was first identified in 1999 in a large outbreak in Malaysia and Singapore which was caused by

transmission from infected pigs to humans. Since then, outbreaks have occurred almost annually in Bangladesh with human-to-human spread. The virus has the potential to cause large outbreaks. There are no approved treatments or vaccines.

This study is of a vaccine called ChAdOx1 NipahB which has been developed by The University of Oxford. The vaccine is similar to the Oxford/AstraZeneca COVID-19 vaccine, however, the trial vaccine targets a component of the Nipah virus rather than the virus that causes COVID-19. This trial will be the first time the vaccine is given to humans. The purpose is to assess the safety and immune response.

We will recruit 51 healthy people aged 18 to 55 years. Participants will be screened for eligibility with an online questionnaire and telephone call, followed by an in-person medical assessment. The first 6 eligible participants will have two doses of vaccine 12 weeks apart. The following 45 participants will be assigned, at random, to one of three groups. Group 1 will receive one dose of vaccine and one dose of sterile salt water, group 2 will receive two doses of vaccine, and group 3 will receive two doses of sterile salt water. The intramuscular injections will be given 12 weeks apart. The sterile salt water has no active ingredients which means it acts as a 'placebo'. Apart from the researchers responsible for the randomisation, preparation and administration of the vaccine, the study team nor the participants will know whether vaccine or placebo were given until the end of the study. Participants will be followed up for 1 year from the first vaccination.

3 SYNOPSIS

Trial Title	A phase I safety and immunogenicity study of a Nipah virus vaccine, ChAdOx1 NipahB, in healthy volunteers aged 18 to 55 in the UK
Trial Site(s)	Site 1 (Recruiting): Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital, Oxford OX3 7LE Site 2 (Non-Recruiting): Oxford University Hospital Foundation Trust Laboratories (OUHFT)
Funder	Coalition for Epidemic Preparedness Innovations (CEPI)
Trial Code	NIV001
Study Design	First-in-human, phase I clinical trial with an initial open-label non-randomised lead-in cohort (cohort 1), followed by a participant-observer blind cohort, 4:4:1 randomised to single-dose ChAdOx1 NipahB, two-dose ChAdOx1 NipahB, or placebo, respectively (cohort 2)
Vaccine Schedule	1 dose given at week 0, or 2 doses given at 0 and 12 weeks
Population	Healthy adults aged 18 to 55 years with no adenoviral-vectored vaccine exposure within the preceding year
Planned Study Size	51 participants (6 in cohort 1; 45 in cohort 2)
Follow-up Duration	12 months
Planned Trial Period	Q3 2023 to Q4 2024
Primary Objective	To assess the safety and tolerability of ChAdOx1 NipahB in healthy adult volunteers
Secondary Objective	To assess the immunogenicity of ChAdOx1 NipahB in healthy adult volunteers
Investigational Products	1. ChAdOx1 NipahB (5×10^{10} viral particles (vp) per dose administration) 2. Placebo comparator: 0.9% sodium chloride (saline) injection
Route	Intramuscularly (IM) into the deltoid region of the arm

Cohort	Group	Number of Participants	Intervention 1 (Week 0)	Intervention 2 (Week 12)	Follow-up Period
1	A	6	5×10^{10} vp ChAdOx1 NipahB	5×10^{10} vp ChAdOx1 NipahB	1 year
2	1	20	5×10^{10} vp ChAdOx1 NipahB	Saline placebo	1 year
	2	20	5×10^{10} vp ChAdOx1 NipahB	5×10^{10} vp ChAdOx1 NipahB	1 year
	3	5	Saline placebo	Saline placebo	1 year

4 SCHEDULE OF PROCEDURES TABLE

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]	0 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) and height and weight	X
Screening physical examination	X
TOPS initial check *www.tops.org.uk*	X
Record emergency contact information	X
Urine Samples	
Highly Sensitive Urinary hCG (WOCBP only)	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)

[2]Medical history may be initially assessed by a telephone call prior to screening (section 9.2)

[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 abnormality in the results)

TOPS: The Over-volunteering Prevention System; WOCBP: women of child bearing potential

4.2 Schedule of Procedures Table: Vaccination and Follow up Visits (Cohort 1)

Table 2 Schedule of Procedures Table: Vaccination and Follow up Visits (Cohort 1)

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
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
Timeline[1]	D0	D2	D7	D14	D28	D56	V2 (D84)	V2 +2	V2 +7	V2 +14	V2 +28	V2 +56	V2 +281
Time window (days)		±1	±2	±3	±3	±7	±14	±1	±2	±3	±3	±7	±60
Visit Procedures													
Review contraindications, inclusion and exclusion criteria	X						X						
Vaccination (and immediate post-vaccination observation period)	X						X						
Vital signs (heart rate, temperature, blood pressure)	X	X	X	X	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)	(X)	(X)	(X)
Adverse Event Collection													
Solicited AE collection	D0 to D6						V2 to V2+6 days						
Unsolicited AE collection	D0 to D27						V2 to V2+27 days						
SAEs & AESI collection	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
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													
Highly Sensitive Urinary hCG (WOCBP only)	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	~5	~5	
Immunology (mL)	~60			~60	~50	~50	~50			~60	~70	~50	~50
Blood volume per visit (mL)	~69	~5	~5	~65	~55	~55	~55	~5	~5	~65	~75	~55	~50
Cumulative blood volume (mL)	~79	~84	~89	~154	~209	~264	~319	~324	~329	~394	~469	~524	~574

[1]Additional unscheduled visits may occur (for example: to repeat a blood test or 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)

WOCBP: women of child bearing potential

4.3 Schedule of Procedures Table: Vaccination and Follow up Visits (Cohort 2)

Table 3 Schedule of Procedures Table: Vaccination and Follow up Visits (Cohort 2)

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit type	Vac1	f/u	f/u	f/u	Vac2	f/u	f/u	f/u	f/u
Timeline[1]	D0	D1	D14	D28	V2 (D84)	V2+1	V2+14	V2+28	V2+281
Time window (days)		+1	±3	±3	±14	+1	±3	±3	±60
Visit Procedures									
Review contraindications, inclusion and exclusion criteria	X				X				
Randomisation	X								
Vaccination (and immediate post-vaccination observation period)	X				X				
Vital signs (heart rate, temperature, blood pressure)	X	X	X	X	X	X	X	X	
Targeted medical history/physical examination, if required	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse Event Collection									
Solicited AE collection	D0 to D6				V2 to V2+6 days				
Unsolicited AE collection	D0 to D27				V2 to V2+27 days				
SAEs & AESI collection	X	X	X	X	X	X	X	X	X
Review ongoing AEs		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									
Highly Sensitive Urinary hCG (WOCBP only)	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	
Immunology (mL)	~60		~60	~50	~50		~60	~70	~50
Blood volume per visit (mL)	~69	~5	~65	~55	~55	~5	~65	~75	~50
Cumulative blood volume (mL)	~79	~84	~149	~204	~259	~264	~329	~404	~454

[1]Additional unscheduled visits may occur (for example: to repeat a blood test or 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). WOCBP: women of child bearing potential

5 BACKGROUND & RATIONALE

5.1 Impact of Nipah and the Need for a Vaccine

Nipah virus (NiV) has been identified as an emerging outbreak pathogen by the World Health Organization (WHO),[1] the US National Institute of Allergy and Infectious Diseases (NIAID),[2] and the UK Health Security Agency (UKHSA),[3] which classifies it as a high consequence infectious disease.

NiV is a zoonotic virus. It was first identified in Malaysia in 1999 following an outbreak of severe respiratory disease in pigs, which led to 265 human cases of respiratory and neurological disease (encephalitis) with 105 deaths.[4,5] The outbreak spread to Singapore where it infected 11 abattoir workers who were in contact with infected imported pigs. The overall case fatality rate of the outbreak was 40%.[6] Since then, outbreaks have occurred in parts of India such as Kerala,[7] the Philippines,[8] and almost annually in Bangladesh. The case fatality rates from these outbreaks is between 75-100%. Up to 2018, there have been an estimated 639 human cases diagnosed and reported (265 from Malaysia, 261 Bangladesh, 85 from India, 17 from the Philippines, and 11 from Singapore).[9]

NiV is part of the *Henipavirus* genus and the *Paramyxoviridae* family. It is a single-stranded enveloped RNA virus. NiV is related to, but distinct from, Hendra virus, first identified in Australia in 1994.[10] Hendra virus causes severe respiratory and neurological disease in horses with some horse-to-human transmission. Two distinct clades of NiV have been identified: the Malaysian strain (NiV_M) which caused the original outbreak, and the Bangladesh strain (NiV_B) which has been responsible for subsequent outbreaks.[11] The attachment glycoprotein (G) and the fusion glycoprotein (F) mediate cellular attachment and host cell entry via class B ephrins which are expressed in large numbers in airway epithelia and neural cells.[12] Anti-G antibody is thought to be an important neutralising antibody.[13]

Fruit bats of the *Pteropus* genus are the natural animal reservoir of NiV.[14] The virus is secreted in bat saliva and urine. In the Malaysian outbreak, bat secretions probably contaminated pig feed, which then led to pigs becoming infected as intermediary hosts.[15] This led to pig-to-pig transmission through infected urine, saliva and respiratory secretions, and onward pig-to-human infection.[6] The main route of transmission for subsequent outbreaks has been from human consumption of contaminated fruits including mango and raw date palm sap,[16,17] with close-contact human-to-human transmission.[18,19] One of the concerning features of NiV is its broad species tropism, which includes cats, dogs and ferrets in addition to pigs and humans.[20]

The incubation period of cases from the Malaysia outbreaks was 4 days to 2 months, whereas the incubation period during Bangladesh outbreaks seem to be shorter at 6 to 11 days.[21] The age distribution has varied between individual outbreaks, with cases reported from 2 to 60 years of age.[21] The clinical spectrum of disease ranges from asymptomatic infection to severe febrile encephalitis, characterised by headaches, vomiting, seizures and altered consciousness. NiV can also cause severe respiratory problems requiring intensive management. There are currently no approved vaccines or specific treatments available for NiV infection, and clinical management is focused around supportive care.

5.2 Rationale for Vaccination

This virus continues to cause regular outbreaks. With a broad species tropism and human-to-human transmission, it has the potential to cause very large outbreaks. With no approved vaccines or treatments and a very high case fatality rate, NiV presents a major threat to global health. To this end, we have developed ChAdOx1 NipahB, a simian adenoviral-derived replication incompetent viral vector vaccine encoding the NiV Bangladesh strain G glycoprotein. This vaccine could be used in the context of outbreaks or administered within routine national immunisation programmes. In parallel, the vaccine is also being developed and tested for use in pigs.

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 a number of clinical trials[22-25] with over 2 billion doses administered to date.

5.3 ChAdOx1 NipahB Vaccine

5.3.1 ChAdOx1 Vector and ChAdOx1 NipahB

ChAdOx1 is a recombinant simian adenovirus viral vector developed by the University of Oxford. It was derived from wildtype serotype Y25 adenovirus which has been rendered replication-deficient through deletion of the E1 gene region which is essential for viral replication. ChAdOx1 NipahB consists of the ChAdOx1 vector encoding the NiV attachment glycoprotein G. The glycoprotein sequence used in the vector is from NiV-Bangladesh isolated from an outbreak Bangladesh between 2008-2010 (Genbank accession number: JN808864.1). Due to its role in viral attachment, the NiV-Bangladesh G glycoprotein has been chosen as the target antigen for use in ChAdOx1 NipahB and by the majority of other NiV vaccines that are currently in clinical development (section 5.4).

5.3.2 ChAdOx1 NipahB Pre-Clinical Studies

An immunogenicity study was conducted in mice in 2018 (UK study, unpublished). Ten mice were immunised with a single IM dose of 10^8 IU ChAdOx1 NipahB (referred to as ChAdOx1 NiV G in the data figures below) and 10 control mice were immunised with an adjuvant only. This demonstrated that the vaccine was immunogenic in mice, and that neutralising antibodies continued to increase between days 21 and 42 (the study end-point) following a single vaccine dose (Figure 1).

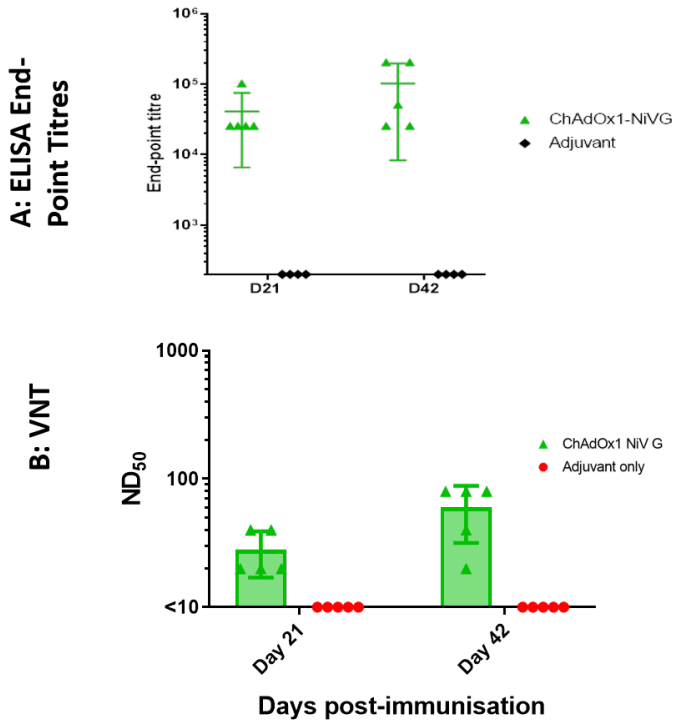

Figure 1 Mice were vaccinated on day 0 with ChAdOx1 NipahB (ChAdOx1 NiV G) at 10^8 IU IM (n=10) or adjuvant only (n=10). **A:** ELISA end-point tires at day 21 (n=5) and day 42 (n=5) after vaccination. **B:** Virus neutralising titres (VNT) at day 21 (n=5/group) and day 42 (n=5/group) after vaccination. VNT assays were completed using live NiV-Malaysia. Bars represent mean values±SD.

An efficacy (challenge) study was performed in Syrian golden hamsters.[26] Four groups of 10 hamsters were vaccinated with either ChAdOx1 NipahB prime-only, ChAdOx1 NipahB prime-boost (28 days between doses), ChAdOx1 GFP control (ChAdOx1 expressing the irrelevant GFP antigen) or saline control. Vaccine doses were administered IM at a dose of 100 µl of 10^8 IU. Prior to challenge, neutralising antibodies were higher in the prime-boost group than the prime-only animals (Figure 2).

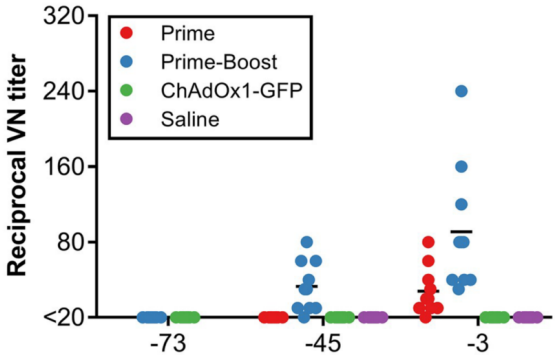

Figure 2 Virus neutralising (VN) antibodies in serum determined via viral neutralisation assay (VeroE6 cells) at days -73, -45 and -3 (prior to viral challenge) in Syrian golden hamsters vaccinated with either ChAdOx1 NipahB prime-only (n=10), ChAdOx1 NipahB prime-boost (28 days between doses, n=10), ChAdOx1 GFP control (prime-boost, n=10) or saline control (prime only, n=10). Vaccine doses were a total of 100 µl of 10^8 IU of each prime and boost administrations, given IM. Bars represent mean values.

The hamsters were then challenged 42 days later with a uniformly lethal intraperitoneal dose of Nipah-Bangladesh (5.3 x 10^5 $TCID_{50}$). Vaccinated animals survived with no signs of disease (including prime-only), whereas control animals lost weight and died between day 6 and 10 after challenge

(Figure 3). Oropharyngeal swabs were taken daily and assessed for infectious virus. None of the vaccinated animals had detectable infectious virus at any point, whereas the animals in the two control groups had detectable infectious virus at days 5 and 6.

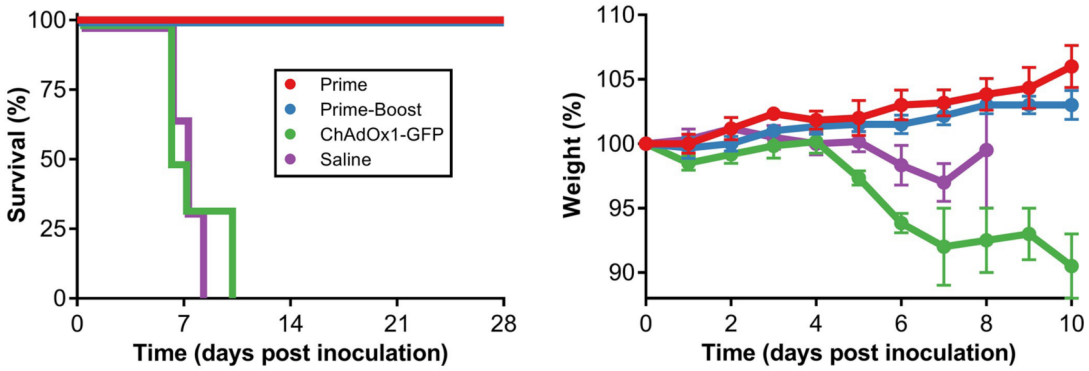

Figure 3 Survival and weight loss in hamsters (n=10/group) following challenge with a uniformly lethal intraperitoneal dose of NiV-Bangladesh (5.3 x 10^5 $TCID_{50}$) on day 0 (42 days after final vaccine administration). Hamsters were vaccinated with either ChAdOx1 NipahB prime-only, ChAdOx1 NipahB prime-boost (28 days between doses), ChAdOx1 GFP control (prime-boost) or saline control (prime-only). Vaccine doses of 100µl of 10^8 IU were administered IM.

In a second challenge study, groups of 10 hamsters were vaccinated with a prime-only dose of ChAdOx1 NipahB (n=6) or control ChAdOx1 GFP (n=4). They were challenged 28 days following vaccination with a lethal dose of intraperitoneal NiV-Malaysia (6.8 x 10^4 $TCID_{50}$). All vaccinated animals survived with no evidence of disease (until euthanasia at day 28), whereas all control animals died between day 5 and 6 following weight loss and neurological signs. When Hendra virus was used as the challenge agent (6.0 x 10^3 $TCID_{50}$), 4 of 6 vaccinated animals died between day 5 and 7 (with the survivors remaining well with <2% weight loss), whereas the 4 control animals died between day 4 and 6. Taken together, these results suggest that both a prime-only and a prime-boost regimen of ChAdOx1 NipahB protected hamsters against lethal challenge with NiV-Bangladesh. A single vaccination was protective against NiV-Malaysia but was only partially protective against Hendra challenge.

A non-human primate efficacy study was performed in African green monkeys.[27] Three groups of monkeys (n=4 per group) were vaccinated with ChAdOx1 NipahB prime-only, prime-boost (days 56 and 28 before challenge, 28 days apart), or ChAdOx1 GFP control at a dose of 2.5 x 10^{10} VP administered IM. NiV G-specific IgG antibodies and NiV G-specific T cell responses were detected on day 14 after vaccination and the day of challenge; these were significantly increased in the prime-boost group compared to the prime-only group (Figure 4). This demonstrated that both the prime-only and prime-boost regimen stimulate an adaptive immune response, with evidence of boosting effect in those administered two vaccine doses.

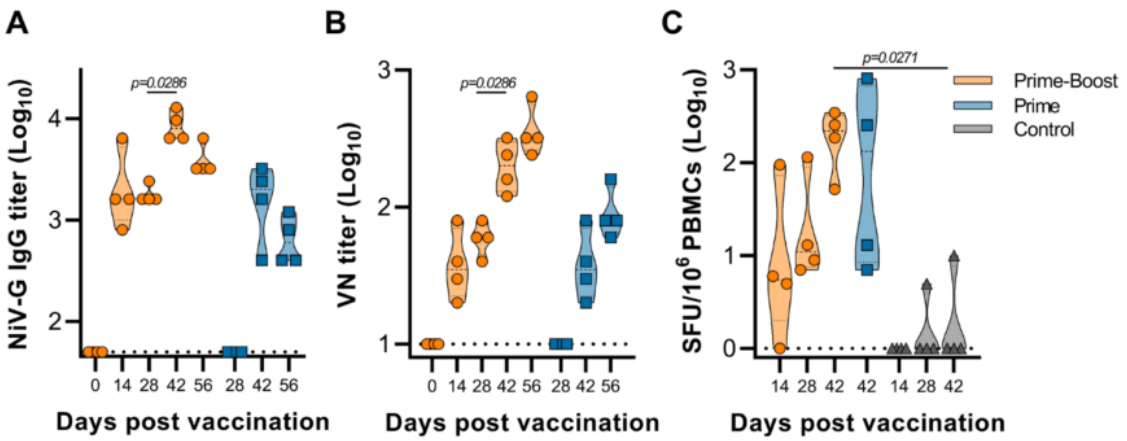

Figure 4 African green monkeys were vaccinated with ChAdOx1 NipahB prime-only (n=4), prime-boost (n=4, 28 days apart), or ChAdOx1 GFP control (n=4) at a dose of 2.5 x 10^{10} VP administered IM. **A**: NiV G-specific IgG in serum after prime-only, prime-boost or control vaccination. **B:** Neutralising viral titres. **C**: NiV-G protein-specific T cell responses in PMBC. SFU: Spot forming units.

Animals were challenged with Nipah-Bangladesh (2 x 10^5 $TCID_{50}$, via the intranasal and intratracheal route), 28 days following vaccination. Animals in the control group started to develop clinical signs at day 3 post-challenge and all 4 animals were euthanized between days 5 to 7. There were no signs of disease observed in either prime-only or prime-boost group animals (until study end-point at day 42 post-challenge). Infectious virus could be detected in nose and throat swabs of 3 of 4 control animals, whereas those from vaccinated animals (prime-only and prime-boost) were negative (except for one throat swab obtained at day 3 post-challenge in a prime-boost animal).

This study shows that although a prime-boost regimen resulted in a higher level of NiV IgG-specific G antibodies and T cell responses, a single dose of ChAdOx1 NipahB was fully protective against a lethal challenge with NiV-Bangladesh in African green monkeys. There was little evidence of virus recovery from daily nose and throat swabs in vaccinated animals.

Five studies in pigs have been conducted. These studies are important not only for the pre-clinical development of the ChAdOx1 NipahB vaccine but also its development for use in pigs. The first study was an immunogenicity study conducted in 2018 (UK study, unpublished). Nine pigs were vaccinated with ChAdOx1 NiV G though a prime-boost regimen of 10^9 IU administered IM on days 0 and 21. Control pigs were vaccinated with an adjuvant only. There was evidence of increased titres of anti-NiV G-specific antibodies and neutralising virus titres on day 41 compared with day 20 in vaccinated pigs (Figure 5). T cell responses peaked at around day 28 (7 days after booster vaccination).

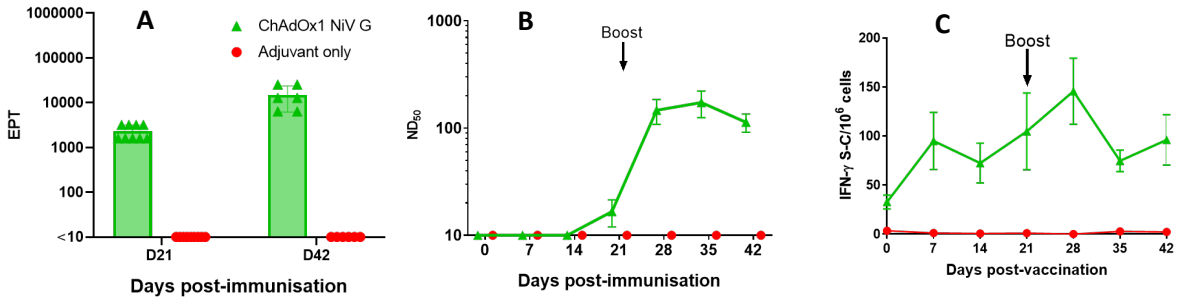

Figure 5 Nine pigs were vaccinated with ChAdOx1 NipahB (ChAdOx1 NiV G) as a prime-boost regimen of 10^9 IU administered IM on days 0 and 21, with 9 controls given adjuvant only. **A**: ELISA end-point titres (EPT) on days 20 (n=9 vaccinated pigs) and day 41 (n=6 vaccinated pigs). ELISA EPTs are NiV G-specific. **B**: Viral neutralisation titres were completed using live NiV-Malaysia. **C**: T cell response as measured by IFNg ELISpot. Cells stimulated with peptide pool representing NiV G. Mean values±SD.

A second immunogenicity study was conducted in 2021 (UK study, unpublished). This study was designed to compare the immune response in pigs receiving a prime-only (n=5) and prime-boost (n=5) regimen of ChAdOx1 NipahB. Pigs were vaccinated with 10^9 IU administered IM (with two doses 21 days apart in the prime-boost group). There was evidence of boosting of the NiV G-specific IgG antibodies and neutralizing viral titres in the prime-boost pigs compared to the prime-only animals, however the levels were the same between the two groups by the study end-point of day 112 (Figure 6). The T cell response was boosted in the prime-boost pigs and a higher level persisted than in the prime-only pigs until the end of the study (Figure 6).

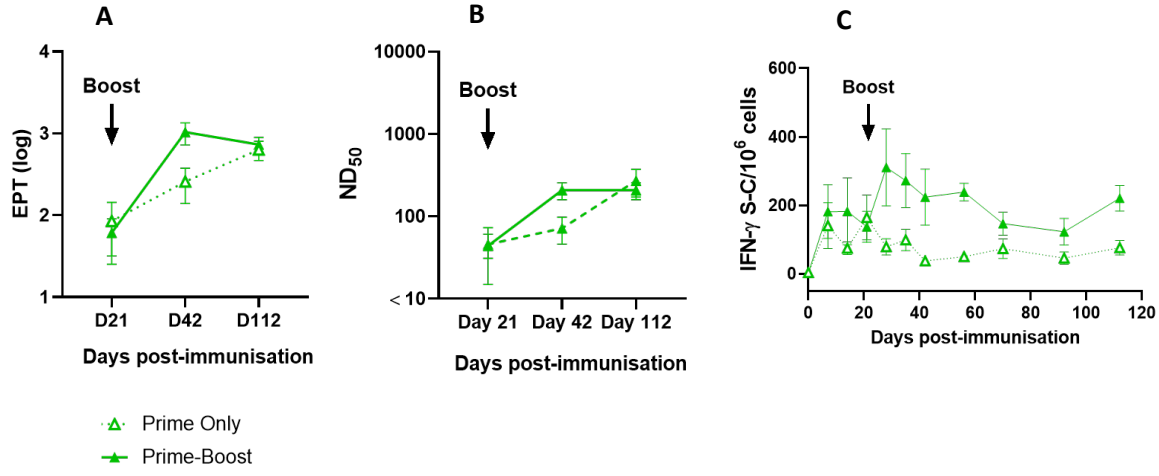

Figure 6 A: ELISA end-point titres (EPTs) in pigs vaccinated with 10^9 IU ChAdOx1 NipahB IM as part of a prime-only (n=5) or prime-boost (n=5) regimen given on days 0 and 21. ELISA EPTs are NiV G-specific. **B**: Viral neutralisation titres completed using live NiV-Malaysia. **C**: T cell response as measured by IFNg ELISpot. Cells stimulated with peptide pool representing NiV G. Mean values±SD.

An efficacy study was conducted in pigs in 2019 (Australian study, unpublished). Three pigs were vaccinated with 10^9 IU of ChAdOx1 NipahB administered IM on days 0 and 21, with another group of 3 pigs vaccinated with two doses of adjuvant only. The pigs were then challenged with NiV-Malaysia at a dose of 5 x 10^4 given oronasally, administered on day 42 (21 days after the booster dose). Pigs were euthanised on day 6 post-challenge because this is expected peak in viral infection and NiV does not reliably induce clinical signs following challenge. There were no clinical signs post-vaccination or

post-challenge in either group of animals. There was evidence of increasing viral neutralisation titres during the study up until the point of NiV-Malaysia challenge (Figure 7).

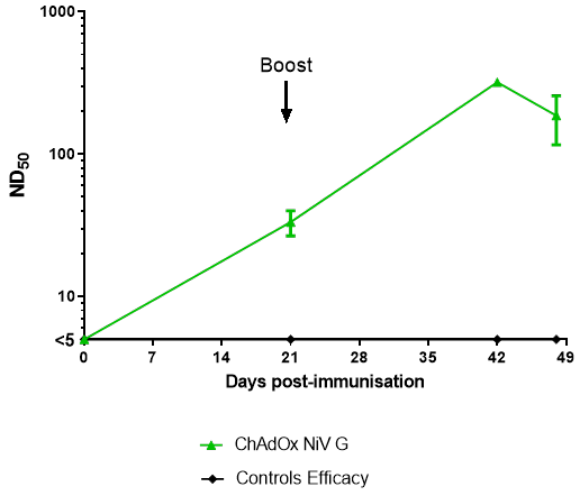

Figure 7 Viral neutralisation titres (VNT) in pigs administered a prime-boost regimen of ChAdOx1 NipahB (ChAdOx NiV G) on days 0 and 21 (n=3, 10^9 IU given IM) compared to pigs administered two doses of adjuvant only (n=3). Pigs were challenged with NiV-Malaysia at a dose of 5 x 10^4 $TCID_{50}$ given oronasally on day 42. Pigs were euthanised on day 49. VNT completed using live NiV-Malaysia.

There was no virus isolated in oral, nasal or tissue specimens in the vaccinated group, whereas in the control group, virus was isolated on nasal swabs on days 5 and 6 post-challenge, and some post-mortem tissue specimens (Figure 8). RNA was isolated at low levels in post-mortem tissues and oral swabs of vaccinated pigs at 5- and 6-days post-challenge but at lower levels than control pigs (Figure 8). It was not detected in nasal swabs whereas in control pigs this was detected from day 3 onwards.

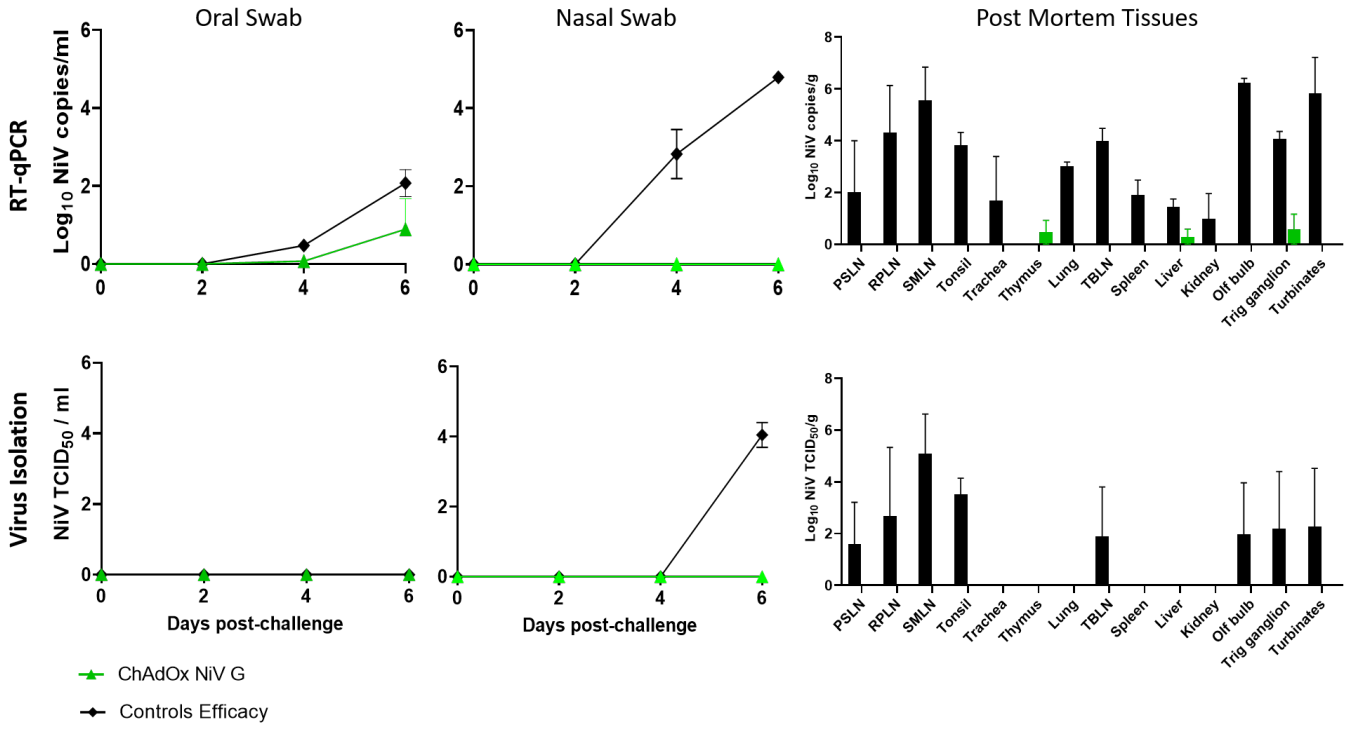

Figure 8 RT-qPCR and viral isolation (by growth on Vero cells) on daily oral and nasal swabs, as well as post-mortem tissues, in pigs administered a prime-boost regimen of ChAdOx1 NipahB (ChAdOx NiV G) on days 0 and 21 (n=3, 10^9 IU given IM) compared with pigs administered two doses of adjuvant only (n=3). Pigs were challenged with NiV-Malaysia at a dose of 5 x 10^4 $TCID_{50}$ given oronasally on day 42. Pigs were euthanised on day 49.

A second efficacy study was conducted in pigs in 2021 (Australian study, unpublished). The purpose of this study was to determine if a prime-only regimen would be sufficient to protect pigs from viral challenge. Three pigs were vaccinated with 10^9 IU of ChAdOx1 NipahB administered IM and 3 pigs were vaccinated with adjuvant only. Pigs were then challenged with NiV-Malaysia at a dose of 5 x 10^4 $TCID_{50}$ oronasally 21 days after vaccination. Pigs were euthanised on day 6 post-challenge (day 27). There were no clinical signs post-vaccination or post-challenge in either group of animals. There was evidence of increasing viral neutralisation titres during the study, including beyond the point of NiV-Malaysia challenge (Figure 9).

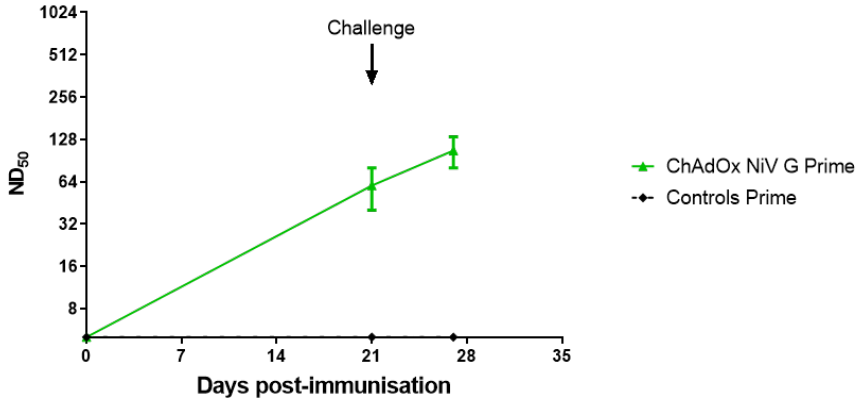

Figure 9 Viral neutralisation titres (VNT) in pigs administered a prime-only regimen of ChAdOx1 NipahB (ChAdOx NiV G) on day 0 (n=3, 10^9 IU given IM) compared with pigs administered adjuvant only (n=3). Pigs were challenged with

NiV-Malaysia at a dose of 5 x 10^4 $TCID_{50}$ given oronasally on day 21. Pigs were euthanised on day 27. VNT completed using live NiV-Malaysia.

There were similar levels of NiV copies in oral, nasal and rectal swabs between vaccinated pigs and controls on each day post challenge, as well as similar levels of in post mortem tissues between vaccinated and control pigs (Figure 10). Virus isolation data are currently unavailable. This data suggests that a single dose ChAdOx1 NipahB did not reduce viral infection in pigs following challenge compared with unvaccinated pigs.

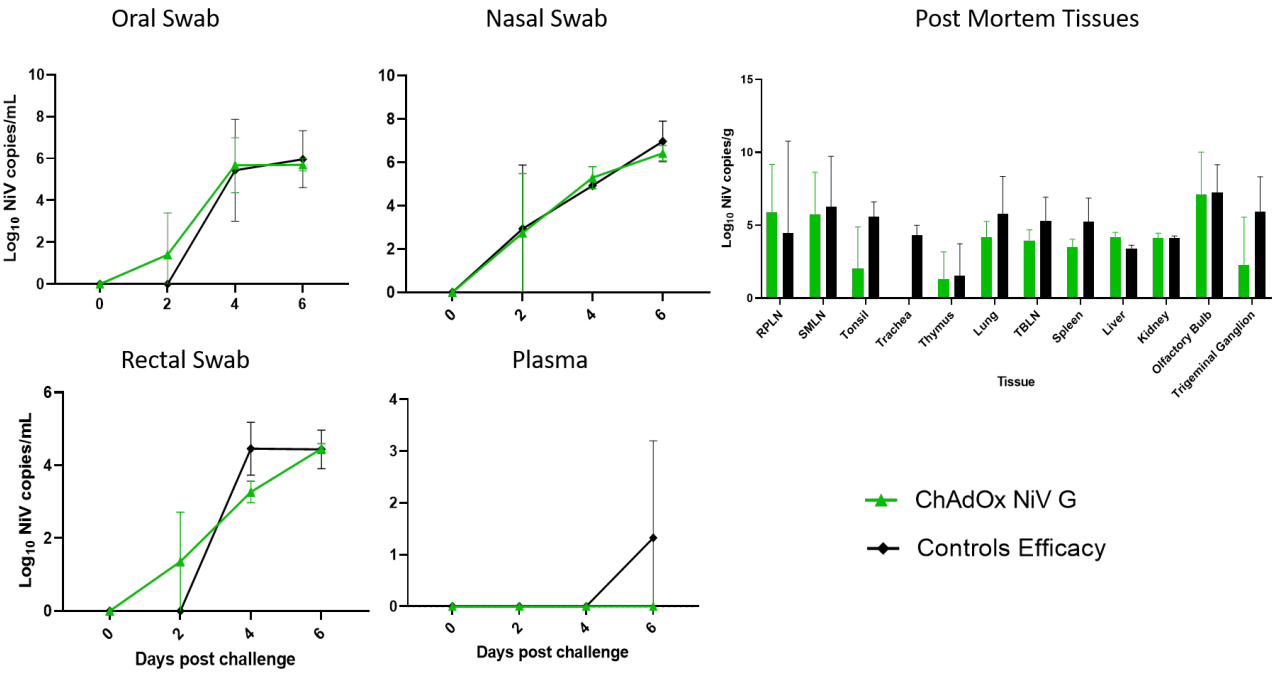

Figure 10 RT-qPCR daily oral, nasal and rectal swabs, plasma and post-mortem tissues, in pigs administered a prime-only regimen of ChAdOx1 NipahB (ChAdOx NiV G) on day 0 (n=3, 10^9 IU given IM) compared with pigs administered adjuvant only (n=3). Pigs were challenged with NiV-Malaysia at a dose of 5 x 10^4 $TCID_{50}$ given oronasally on day 21. Pigs were euthanised 6 days after viral challenge.

The final study in pigs was an immunogenicity study to evaluate a prime-boost regimen of ChAdOx1 NipahB in indigenous pigs reared in free-scavenging systems in Bangladesh (2021 study, unpublished). Along with ChAdOx1 NipahB, another vaccine called NiV mscF (cell fusion glycoprotein) was included in this study which provided a comparison cohort. Seven villages in 3 clusters were included in the study, with 5 pigs from each cluster and a total of 15 pigs per vaccine. This showed that indigenous pigs were able to mount an antibody response with evidence of boosting, and that antibody titres and viral neutralisation was comparable to pigs under laboratory conditions from the 2018 immunogenicity study (Figure 11).

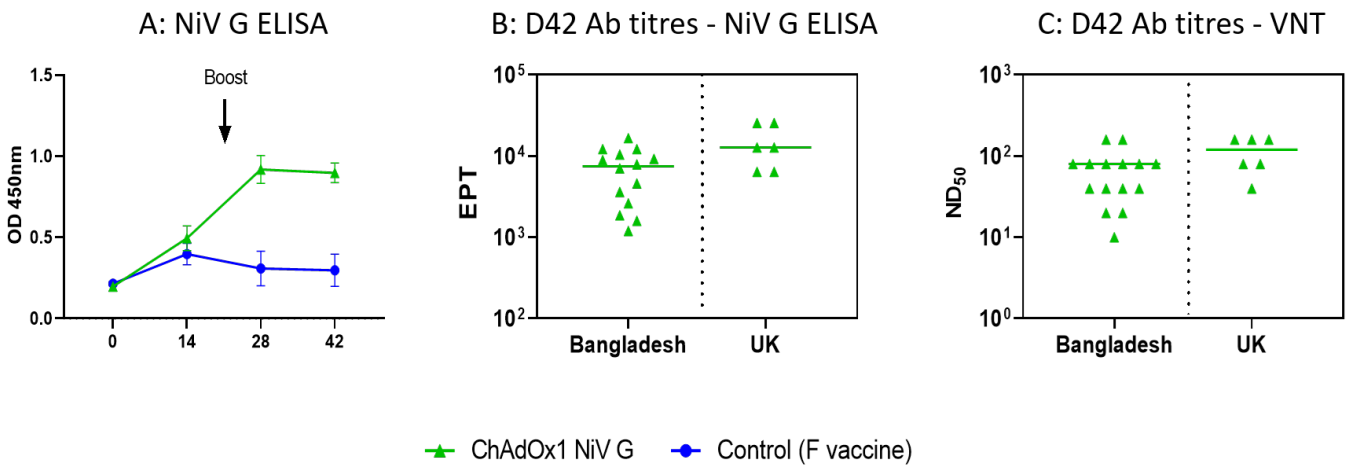

Figure 11 Indigenous pigs from Bangladesh were administered a prime-boost regimen of ChAdOx1 NipahB (ChAdOx NiV G) on days 0 and 21 (n=15, 10^9 IU given IM) or two doses of a comparison vaccine (NiV mscF, n=15). **A**: ELISA end-point titres (NiV G-specific) following vaccination. Mean values±SD. **B**: Day 42 ELISA antibody titres were compared between Bangladesh pigs (n=15) and the pigs from the 2018 pig immunogenicity study (n=6, also administered the same prime-boost regimen). Bars presents mean values. **C**: Virus neutralisation titres (VNT) in Bangladesh pigs (n=15) and UK pigs (n=6) completed using live NiV-Malaysia. Bars presents mean values.

5.3.3 ChAdOx1 NipahB Toxicology Study

A repeat dose GLP toxicology study (Labcorp, 8506431) in Balb/c mice of a two-dose schedule of ChAdOx1 NipahB at 1 x 10^{10} vp IM with a 14-day interval and 2-week recovery concluded that ChAdOx1 NipahB was well tolerated and not associated with adverse events. The toxicology summary is further summarised in the Investigator's Brochure.

5.3.4 ChAdOx1 NipahB Clinical Studies

To date, there have been no clinical studies of ChAdOx1 NipahB and therefore the proposed study is a first-in-human study.

5.4 Other NiV Vaccines in Pre-clinical Testing

As of April 2021, there are 44 *Henipavirus* vaccines with published data in pre-clinical development, of which 8 are planned for veterinary use.[28] Nineteen of these vaccines use viral vectors. Surface G and F proteins are the immunogens most frequently used, and published data to date suggest these vaccines are highly immunogenic in animal models. Degrees of protection against homologous and heterologous *Henipavirus* strains have been demonstrated in animal challenge studies using African green monkeys, Syrian golden hamsters and ferrets.

A toxicology study of a live, replication competent recombinant vesicular stomatitis virus-vectored vaccine (PHV02) was published in June 2022.[29] This vaccine expresses two envelope glycoproteins: EBOV (Ebola virus, which on its own constitutes the approved Ervebo vaccine) and the NiV G attachment glycoprotein. Due to the neurotropic nature of NiV and the use of a live replication competent viral vector, toxicology studies included investigation of neurovirulence/neuroinvasiveness. The study used the Ervebo vaccine and an approved yellow fever vaccine (which has residual neurotropism) as comparators. PHV02 was neurovirulent in infant mice and hamsters following intracerebral inoculation. In adult hamsters, neurovirulence was

demonstrated at a high median lethal dose, but in adult mice, the vaccine was non-pathogenic. The study progressed to monkeys due to this animal mode being considered the gold standard for neurovirulence and because of the mixed results in mice and hamsters. PHV02 was less neurovirulent in monkeys compared to the yellow fever control (which has known residual neurotropic adverse event profile in humans). PHV02 has been taken forward into phase 1 clinical trials, with results of this pending.

5.5 Other NiV Vaccines in Clinical Testing

The International Clinical Trials Registry Platform was searched on 23rd February 2023 for "Nipah". Three experimental Nipah vaccines in phase I clinical trials were identified. These are summarised in Table 4 Nipah Vaccines in Registered Clinical Trials (23rd February 2023). Each of the three previously registered trials use a different vaccine technology. There are no adenoviral-vectored vaccines currently in clinical trials. As yet, there are no published clinical data of NiV vaccines.

Table 4 Nipah Vaccines in Registered Clinical Trials (23rd February 2023)

Vaccine technology	Vaccine Name	Manufacturer	Trial Phase	Registration number, year of registration	Results
mRNA vaccine	mRNA-1215	Moderna	Phase 1	NCT05398796, 2022	Not available (trial recruiting)
Live recombinant vesicular stomatitis virus vector vaccine	PHV02*	Public Health Vaccines LLC	Phase 1	NCT05178901, 2021	Not available (trial recruiting)
Recombinant subunit vaccine	HeV-sG-V	Auro Vaccines LLC	Phase 1	NCT04199169, 2019	Not available (recruitment completed)

*Note that the discussion of the toxicology study under the section 5.4 Other NiV Vaccines in Pre-clinical Testing corresponds to this vaccine.

5.6 Previous Clinical Experience with Other ChAdOx1 Vaccines

A number of other ChAdOx1 vectored vaccines have also been developed and tested in clinical trials, most notably the ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine) which has been approved in many countries with over 2 billion doses administered worldwide.[23-25,30,31]

Early phase clinical trials have also been performed for a number of other ChAdOx1 vectored 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, with positive safety and immunogenicity results.[32,33] Further details of other ChAdOx1 clinical studies are contained within the ChAdOx1 NipahB Investigator Brochure.

5.7 Rationale for Selected Doses

The regimen and dose of ChAdOx1 NipahB (5 x 10^{10} viral particles per dose, as either a single or two-dose administration) was selected on the basis of pre-clinical and clinical experience with other ChAdOx1 vaccines, as well as other adenovirus vaccines.

The ChAdOx1 NipahB pre-clinical toxicology study (Labcorp 850643, carried out using the engineering batch, summarised in the ChAdOx1 NipahB Investigator's Brochure) supports the clinical evaluation of ChAdOx1 NipahB in a two dose 12-week schedule as in this clinical trial, in line with WHO guidelines on non-clinical evaluation of vaccines.[34] BALB/c mice were administered 1 x 10^{10} IM of ChAdOx1 NipahB with a 2-week dose interval and a 2-week recovery period. This dose was well tolerated and not associated with any clinically important treatment-related adverse effects.

Seventeen ChAdOx1 vectored-vaccines expressing different immunogens have been administered in clinical trials at doses ranging from 5 x 10^{8} to 5 x 10^{10} (the maximum dose tested). A summary of these trials is listed in the appendix of the ChAdOx1 NipahB Investigator's Brochure. Recent phase 1 clinical trials of ChAdOx1 vaccines for Ebola, MERS, Chikungya, Zika and Rift Valley Fever have each included participants immunised with 5 x 10^{10} viral particles (following dose escalation within each of these trials). In every case, the safety and immunogenicity profiles were acceptable for the 5 x 10^{10} viral particle dose, including when this dose was given as a two-dose regimen as in the EBL07 ChAdox1 biEBOV phase 1 trial.

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] Experience with ChAdOx1 nCoV-19 showed that 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.[23,35,36] Real-world studies have demonstrated efficacy following a both a single and two-dose regimen.

Another simian adenovirus vector (ChAd63) has been safely administered at doses up to 2 x 10^{11} vp with an optimal dose of 5 x 10^{10} vp, balancing immunogenicity and reactogenicity.

The African green monkey challenge study described above in section 5.3.2 included a prime-only and prime-boost regimen (28 days apart) of 2.5 x 10^{10}. This demonstrated evidence of boosting following the second vaccine dose, with all animals (both in the prime-only and prime-boost groups) protected from clinical disease.

Based on these data, this study will include both a single and 2-dose regimen of ChAdOx1 NipahB, each containing 5 x 10^{10} viral particles. The 2-dose regimen incorporates a 12-week interval between doses. It is important to investigate the immunogenicity following one dose, as this vaccine could be used in a reactive outbreak setting where a single dose, able to elicit rapid and sufficient protective immunity, would be ideal. The vaccine could also be given in a preventive context, where a two-dose schedule may be required to stimulate longer-lasting immunity. It is important compare the immune responses between a single and 2-dose schedule for these reasons.

5.8 Potential Risks to Participants

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

5.8.1 ChAdOx1 NipahB-Related Risks

The most likely side effects that recipients of ChAdOx1 NipahB may experience are short-lived local reactions (primarily injection site tenderness or pain) and systemic reactions (fatigue, headache, malaise, feverishness) that resolve completely within days.

Very rare serious reactions have been identified as part of post-marketing surveillance of ChAdOx1 nCoV-19 (Oxford/AstraZeneca COVID-19 vaccine). These include thrombosis with thrombocytopenia (TTS), immune thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), transverse myelitis, capillary leak syndrome (CLS), and anaphylaxis. It is currently unknown whether these very rare reactions occur with other ChAdOx1 vaccines. As ChAdOx1 NipahB is similar 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 ChAdOx1 NipahB would be harmful to women or the foetus during pregnancy. However, as yet there are no data on the use of ChAdOx1 NipahB in pregnancy. Therefore, pregnant women will be excluded from the trial and women of childbearing potential will be required to use effective contraception to take part (section 8.4).

5.8.2 Other Trial-Related Risks

Blood sampling during the trial may cause slight pain, bruising, light-headedness or fainting. The volume of blood given in the trial is less than that taken by regular blood donors over the same period, so should not compromise healthy participants. 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 participants for further investigation. Participants will be informed of these and, with their consent, their general practitioner (GP) will be contacted.

5.9 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 NiV is currently low. Furthermore, ChAdOx1 NipahB clinical efficacy against NiV 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 NiV 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 ChAdOx1 NipahB in healthy volunteers aged 18-55	a) Occurrence of solicited local reactogenicity signs and symptoms	7 days following each vaccination (D0 to D6; V2 to V2+6)
		b) Occurrence of solicited systemic reactogenicity signs and symptoms	7 days following each vaccination (D0 to D6; V2 to V2+6)
		c) Occurrence of unsolicited adverse events (AEs)	28 days following each vaccination (D0 to D27; V2 to V2+27)
		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 Cohort 2: D0, D1, D14, D28, V2, V2+1, V2+14, V2+28
		e) Occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs)	Duration of the study (D0 to V2+281)
Secondary	To assess the immunogenicity of ChAdOx1 NipahB vaccine in healthy adult volunteers aged 18-55	NipahB glycoprotein G-specific serological response as measured by ELISA	Cohort 1: D0, D14, D28, D56, V2, V2+14, V2+28, V2+56, V2+281 Cohort 2: D0, D14, D28, V2, V2+14, V2+28, V2+281
Exploratory[2]	Immunological profiling	a) NipahB neutralising antibody responses measured by live or pseudoneutralisation assays b) NipahB glycoprotein G T cell response measured by IFN-g ELISPOT c) Cellular immune response to Nipah virus measured by ICS, proliferation and/or whole blood assays	Timepoints will be detailed in the laboratory analysis plan
	To assess anti-PF4 antibody levels following vaccination	Change in anti-PF4 antibody level measured by ELISA	D0, D14, V2+14
	To assess anti-vector immunity following vaccination	Binding and/or neutralising antibody responses against ChAdOx1	Timepoints will be detailed in the laboratory analysis plan

[1]Visit and procedure timepoint windows are defined in section 4 (Schedule of Procedures). [2]These exploratory endpoints may be performed; additionally, sample analysis for the completion of exploratory endpoints may be performed under the ethically-approved Oxford Vaccine Centre (OVC) Biobank protocol (REC 21/SC/0161). Further exploratory assays/analyses may be carried out (see section 9.6.2).

7 STUDY DESIGN

This is a participant-observer blind, randomised, placebo-controlled, first-in-human phase I trial to assess the safety, tolerability and immunogenicity of one or two administrations of an intramuscular (IM) ChAdOx1 NipahB vaccine in healthy adults aged 18 to 55 years. There will be an initial unblinded lead-in cohort (cohort 1) of 6 participants, followed by a participant-observer blind cohort of 45 participants, 4:4:1 randomised to single dose ChAdOx1 NipahB, two-dose ChAdOx1 NipahB, or placebo, respectively (cohort 2).

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

7.1 Study Groups

Cohort	Group	Number of Participants	Intervention 1 (Week 0)	Intervention 2 (Week 12)	Follow-up Period
1	A	6	5×10^{10} vp ChAdOx1 NipahB	5×10^{10} vp ChAdOx1 NipahB	1 year
2	1	20	5×10^{10} vp ChAdOx1 NipahB	Saline placebo	1 year
	2	20	5×10^{10} vp ChAdOx1 NipahB	5×10^{10} vp ChAdOx1 NipahB	1 year
	3	5	Saline placebo	Saline placebo	1 year

7.2 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 is defined as the point when all assays providing data for primary and secondary endpoints have been completed.

7.3 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 in the trial once they have been randomised.

7.4 Group Allocation

The first 6 participants recruited to the trial will be enrolled to cohort 1. These 6 individuals will be non-randomly allocated to group A, an open-label lead-in group.

All subsequent participants (n=45) will be recruited into cohort 2 and randomly allocated to either group 1, 2 or 3 using a 4:4:1 randomisation ratio, respectively. Recruitment into cohort 2 will only proceed following the safety review detailed in section 11.22.

7.5 Blinding and Unblinding

Cohort 2 will be conducted in an observer and participant blind fashion. Blinding of treatment allocation will remain until the last volunteer has completed their last visit (LVLV).

There will be dedicated blinded and unblinded study teams. Unblinded study teams are responsible for randomisation and preparation and administration of vaccine, but will not be involved in any outcome assessment. Blinded staff include members of the clinical team who are responsible for assessing and recording outcomes (including the PI and CI). Access to the randomisation and vaccination electronic case report form (eCRF) of the study database will be password-protected and restricted to the unblinded team. Steps to maintain blinding of the investigational medicinal product (IMP) with the use of a placebo are detailed in section 10.3.

In the event that accidental unblinding of any blinded study team member or participant occurs, this would be recorded as a protocol deviation. The participant's data would be considered, for the purpose of the analysis, as unblinded data (from the point of unblinding).

Participants and their General Practitioners (GPs) will receive written notification by letter or email of whether they have received the vaccine or placebo at the time of full study unblinding, once all participants have completed all follow up visits.

Unblinding may also occur at an earlier time point in the event of the occurrence of a serious adverse event (SAE), serious adverse reaction (SAR) or serious unexpected adverse reaction (SUSAR) on discussion with the CI and/or Data Safety and Monitoring Committee (DSMC).

In the case of a medical emergency the study site investigator will have 24/7 access to unblinding of participant(s) by opening the participants' sealed envelope containing their vaccine administration record or via the REDCap randomisation database which will be accessed by a delegated unblinded trial team member and communicated to the study site investigator. The choice of these two methods depends on which is more readily accessible to the investigator at the time.

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 of the following criteria to be eligible for the study:

1. Adults aged between 18 to 55 years (inclusive) at the time of screening.
2. Medically healthy, such that according to investigator judgement, hospitalisation within the study period is not anticipated, and the participant appears likely to be able to remain a study participant through the end of protocol-specified follow-up. Planned elective procedures for pre-existing conditions are allowable.
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. Willing to allow confirmation of past medical history either through: provision of or access to a medical record summary or other medical documentation, or allowing investigators to obtain a copy of their medical history from their GP practice or accessed via electronic patient records.
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. Agreement to refrain from blood donation during the course of the study.
9. *For women of childbearing potential only* (as defined by protocol section 8.4)*:* willing to use effective contraception from one month prior to receiving the first dose of vaccine and for the duration of the study AND have a negative 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 other study 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 are planning to do so within the trial period.
2. Previous receipt of another adenoviral-vectored vaccine (which includes the Oxford/AstraZeneca and Janssen COVID-19 vaccines) within the preceding year.
3. Previous immunisation with an investigational Nipah vaccine.
4. History of previous confirmed or suspected Nipah infection.
5. Administration of immunoglobulins and/or any blood products within three months preceding the planned administration of the vaccine candidate.
6. 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 three months preceding the planned administration of the vaccine candidate).
7. History of anaphylaxis in relation to vaccination.
8. 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 (EDTA or magnesium chloride).
9. History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
10. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
11. History of any serious psychiatric condition likely to affect participation in the study.
12. *For women only:* participants who are pregnant, breastfeeding or lactating, or are planning pregnancy during the course of the study.
13. 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.
14. 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.
15. History of capillary leak syndrome.

16. Moderate, severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, haematological, immunological, endocrine disorder, or neurological illness (note, mild well-controlled co-morbidities in a healthy participant are acceptable as judged by the Investigator)
17. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 14 units per week.
18. Suspected or known injecting drug use within the 5 years preceding enrolment.
19. Detectable circulating hepatitis B surface antigen (HBsAg).
20. Seropositive for hepatitis C virus (antibodies to HCV).
21. Any clinically significant finding on screening that is either unlikely to resolve or does not resolve (for example on repeat testing at the discretion of an Investigator) within the recruitment timeline of the study.

8.2 Temporary Exclusion Criteria

The following applies to both vaccination visits. If the temporary exclusion resolves within the time constraints of the trial visits, 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 stabilise 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 or stabilise prior to a dose of vaccine being administered.
7. Receipt of other vaccines. These must be administered 30 days before or after study vaccines EXCEPT influenza and COVID-19 vaccines which may be given 14 days before or after study vaccines. Receipt of an adenoviral-vectored vaccine would preclude the participant from further trial vaccinations (see Exclusion Criteria 2).
8. 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 Absolute contraindications to further vaccinations

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

1. Any serious adverse reaction (SAR)
2. Current pregnancy

8.4 Pregnancy and Contraception

The viral vector component of the ChAdOx1 NipahB 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 (another ChAdOx1 vaccine). The risk of human teratogenicity/fetotoxicity with ChAdOx1 NipahB is therefore unlikely.

However, the possible adverse effects of the ChAdOx1 NipahB 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 her ongoing consent, she will be followed up for clinical safety assessment until the pregnancy outcome is determined. Her 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.

Women of childbearing potential will be required to use an effective form of contraception. A woman 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.

Contraception should be continued for one month 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:

1. Established use of oral, injected or implanted hormonal methods of contraception.
2. Intrauterine device (IUD).
3. Intrauterine hormone-releasing system (IUS).
4. Barrier methods of contraception (condom or occlusive cap with spermicide).
5. Bilateral tubal occlusion.
6. Vasectomised male partner, if the vasectomised partner is the sole partner for the participant.
7. Sexual abstinence when this is in line with the preferred and usual lifestyle of 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.
8. Exclusive sex with a female partner(s).

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 posters, leaflets, websites, newspapers, radio, public engagement events, and/or social media, using advertising material containing wording from approved study documents to invite participation in the study. Potential participants may be contacted by email, telephone, and/or mail, using an approved invitation letter.

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

For mail-outs via the electoral register, the study team will obtain access to the names and addresses of individuals who are on the open electoral register (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 outlined below:

- **Email campaign**: We may contact representatives of local tertiary education establishments and local employers and ask them to circulate approved posters and a link to the study website by email or hard copy.
- **Healthy volunteers databases**: Direct email and link may be sent to members of the public who have registered their interest in potentially volunteering for clinical trials. These are secure databases where members of the public registered here have given consent to have their details recorded and be contacted expressly for the purpose of being notified when a trial opens for recruitment. They understand this is not a commitment to participating for any trial they are contacted about.
- **Media advertising**: Approved local media, newspaper and website advertisements may be 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 may be placed on study websites and other appropriate platforms for vaccine trial advertising.
- **Social media**: Approved advertisements may be placed on trial 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 may exhibit using stalls or stands at exhibitions and/or fairs, such as University Fresher's Fairs.

- **SMS/text messages**: SMS/text message (or emails) may be sent to potential participants identified by GPs from their databases (which will require Participant Identification Centres [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 envelopes may be sent to every household within certain postcode areas.

Potential participants who are interested in study participation will be able to contact the study team 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, the participant information sheet will be downloaded/viewed via the study website by the potential participant, and/or sent to them via mail or email.

If potential participants are willing to proceed, they will be asked to complete an initial online questionnaire which will include eligibility screening, e-consent to access medical and vaccination records (either via GP or NHS databases) and store personal information, and obtaining relevant medical history and personal information, 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.

Online and telephone initial screening processes are not mandatory as long as all screening information is captured at the point of the full screening and consent visit. In cases such as these, participants medical records should not be accessed until the consent form is signed at the in-person screening visit.

9.2.2 Baseline Assessments at Screening

Once informed written consent has been given, the following baseline assessments are performed and information is collected as part of the assessment of inclusion/exclusion criteria:

- Participant demographics: e.g. age, sex and ethnicity
- Medical history
- Contraception: female participants of childbearing potential are asked if they are willing to use effective contraceptive measures one month prior to vaccination and for the remainder of the study
- Use of concomitant medication and vaccinations (including over the counter medications, vitamins, illicit drug use and herbal supplements)
- Recording of resting pulse, blood pressure, temperature, weight and height
- Physical examination including (but not limited to) cardiovascular, respiratory, abdominal and gross neurological examination
- Urine pregnancy test (females of childbearing potential only, section 8.4); alternatively, hCG may be added to the blood sample for pregnancy testing
- Blood samples for: full blood count, urea and electrolytes, liver function tests, serology for HIV, hepatitis C and hepatitis B

In addition, at this visit, emergency contact details will be collected.

The medical, vaccination, and prescribed medication history are initially based on participant recall. However, with 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 information (including investigation results) are available for a volunteer from a screening visit of another study, these results may be used to assess eligibility. The screening assessment and results must have occurred at the same trial site, have been within the 90 days preceding enrolment in NIV001, and the volunteer should not have been enrolled into the study they were originally screened for.

9.2.3 Prevention of Over-Volunteering

Consent will be requested 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 Screen Failures

The number of participants who complete the online questionnaire and/or telephone screening and do not subsequently progress to the next step of recruitment (in-person screening and informed consent) will be recorded. Participants who have signed the informed consent form but are not subsequently enrolled in the trial will have the reasons for this recorded (for example: ineligible, withdrew consent prior to enrolment). For each of these participants, a minimal set of data will be recorded including demographic details. These details will be reported as required by Consolidated Standards of Reporting Trials (CONSORT) publishing standards.

9.2.5 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 participant information sheet will be made available 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, the potential risks and their obligations. The following general principles will be emphasised:

- Participation in the study is entirely voluntary.
- Decision not to participate involves no penalty or loss of medical benefits.
- The individual 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 de-identified.
- That long term storage of samples after the trial is over is optional and will be covered under the Oxford Vaccine Centre Biobank Study protocol which will be consented to separately.

The individual will have the opportunity to discuss the study with a medically qualified investigator. Written informed consent will be given by the participant as a dated signature. An appropriately trained and delegated clinician who was responsible for discussing consent with the participant will also sign and date the consent document. 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.

9.3 Randomisation

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

The first six participants will be non-randomly enrolled into cohort 1, which is the initial lead-in cohort. After at least seven days from administration of the first dose of vaccine of all participants in cohort 1, subsequent participants will be enrolled to cohort 2 and randomised to receive one dose of ChAdOx1 NipahB and one dose of saline placebo, two doses of ChAdOx1 NipahB, or two doses of saline placebo in a 4:4:1 ratio respectively. Randomisation will be performed using an electronic system within REDCap (or equivalent electronic database).

9.4 Study visits

The procedures to be included in each visit are documented in the schedule of procedures tables (Section 4). Each visit is assigned a time-point and a window period, within which the visit should be conducted. Whether a visit can occur out of window will be decided on a case-by-case basis by the study investigators.

9.4.1 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 verbally confirm continued consent
- Obtain and document interim medical history since the screening visit including medication use and other vaccinations, 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 highly sensitive urinary pregnancy test for females of childbearing potential (section 8.4); alternatively
- Perform blood draw (as per section 9.6)
- Administer vaccine or placebo by IM injection into the deltoid muscle (ideally the non-dominant arm)

- Post-vaccination observation of volunteer for a minimum of 30 minutes following vaccine administration
- On the first vaccination visit (D0), participant is provided access and training to use the electronic diary (eDiary) using the participant's personal email address for the set-up
- Schedule next visit and re-iterate participant requirements such as completion of the eDiary entries
- On the subsequent vaccination visit, review of AEs and SAEs since the last visit

9.4.2 Follow-Up Visits

Follow-up visits are held at the study site (or remotely, if required, see section 9.4.4). Follow-up visits may require the following procedures:

- Review of concomitant medications and other vaccinations since the last visit
- 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 (as per section 9.6)
- Schedule next visit and re-iterate participant requirements such as eDiary entries

9.4.3 Unscheduled Visits

Additional visits or procedures may be performed at the discretion of investigators, for example for further medical history and physical examination, additional blood tests or other investigations if clinically relevant.

9.4.4 Missed Visits

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

9.5 Electronic Diary (eDiary)

Following each vaccination, participants will have access to an eDiary system (using their personal email address) to allow them to self-report solicited and unsolicited AEs. Each participant will be given unique log-in details associated with their study number. Training for this will be given at the first vaccination visit. A paper copy of the diary may be provided to allow for completion in the event of inability to access the online version for any reason. Local site (blinded) 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.

9.6 Participant Samples

9.6.1 Clinical Laboratory Samples

Blood will be drawn (at different time points according to the schedule of procedures, section 4) for the following laboratory tests. The processing and analysis of the blood will be carried out at an accredited local clinical laboratory.

- Haematology:
    - Full Blood Count (Including: Haemoglobin, platelet count, total white cell count, neutrophil count, lymphocyte count, eosinophil count)
- Biochemistry:
    - Urea and Electrolytes (Including: Sodium, Potassium, Urea and Creatinine)
    - Liver Function Tests (Including: ALT, ALP, Bilirubin, Albumin)
- Diagnostic serology (screening only):
    - Screening tests for Hepatitis B, Hepatitis C and HIV infection (Including: HBsAg, HCV antibodies, HIV antibodies)
- Immunology (first 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).

9.6.2 Immunology Samples

9.6.2.1 University of Oxford Research Laboratories

Immunogenicity will be assessed by a variety of immunological assays. As the secondary objective, NipahB glycoprotein G-specific serological response will be measured by ELISA. Exploratory objectives include NipahB neutralising antibody responses measured by live or pseudo neutralising assays, NipahB glycoprotein G T cell response measured by IFN-g ELISPOT, and cellular immune responses to Nipah virus measured by ICS, proliferation and/or whole blood assays.

Other exploratory immunological assays may include changes in anti-PF4 antibodies levels, 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.

9.6.2.2 Other Research Laboratories

Collaboration with other specialist laboratories in the UK, including laboratories at the trial site(s), 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 de-identified. Informed consent for this will be gained from the participants. Immunological assays will be conducted according to local SOPs.

9.6.3 Urine Samples

For female volunteers of childbearing potential only, urine will be tested for human chorionic gonadotrophin (hCG) at screening and immediately prior to each vaccination. Alternatively, hCG blood sampling may be used instead.

9.6.4 Retention of Samples

Participants will be informed that they may opt-in to the Oxford Vaccine Centre Biobank study (REC 21/SC/0161) to allow long-term storage of biological samples collected under the NIV001 protocol for use in possible future research. The OVC Biobank study is covered by a separate study protocol and consent process. Participants will be informed that declining to take part in the OVC Biobank study will not affect their participation in this study. If a participant elects to decline to take part in the OVC Biobank, all of their remaining samples will be destroyed after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

9.7 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 specific study procedures for an individual participant. However, participants should otherwise continue to attend the follow up visit schedule and follow up procedures unless they withdraw consent for this. Such circumstances may include the following non-exhaustive reasons:

- Pregnancy (further details on management of participants who become pregnant are provided in section 8.4)
- 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)

Withdrawal from the study will not result in exclusion of existing data generated by the participant from analysis. Participants can request that their samples are destroyed at any point during or after the study (although data that has already been generated from samples that have been analysed up to that point will be retained). The reason for withdrawal, if given, will be recorded in the eCRF. Participants who withdraw from the trial after randomisation but prior to receipt of their first vaccine dose may be replaced by a further volunteer who will undergo separate randomisation.

9.8 Special Circumstances: COVID-19

9.8.1 Study Conduct/Risk Assessment

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

On the basis of the COVID-19 situation, the Chief Investigator may perform a risk assessment as necessary and this may involve discussion with relevant parties (such as the DSMC and Regulatory Authorities), to determine:

- Appropriateness to initiate vaccinations
- Appropriateness to continue the trial once started
- Necessity to extend trial duration

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

- Pausing further vaccinations
- Modifying study visits and procedures, for example, study visits could be conducted by phone or video calling where appropriate

9.8.2 COVID-19 Infection Control Measures at Visits

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

9.8.3 Participants Isolating

Should a participant be isolating due to an intercurrent illness including COVID-19, and are thus unable to attend a particular scheduled visit(s), a telephone/video consultation may be arranged in order to obtain follow-up safety information, and the visit may be re-scheduled, depending on the timelines.

9.8.4 Participants with Intercurrent Illness Symptoms

Participants who develop intercurrent illness symptoms, including those of COVID-19 with or without test confirmation, must wait to receive a trial vaccine until they feel they have fully recovered. The decision to proceed with subsequent trial vaccinations will be at the discretion of the Investigators, and each individual will be evaluated by a study doctor before proceeding (including physical examination). The trial clinician must deem that the participant has fully recovered and have no symptoms from their illness.

9.8.5 Participants Invited For COVID-19 Vaccination During the Trial

Participants who become eligible for a COVID-19 vaccination will be invited to discuss this with the study team. If agreed by the participant, the trial team will identify a mutually agreeable time to receive a COVID-19 vaccine. If a vaccination offer coincides with a planned trial vaccine, the trial vaccine will be rescheduled to at least 14 days before or after the COVID-19 vaccine, within the allowable visit windows. This is in line with the UK Green Book COVID-19 vaccination recommendations for other vaccines which recommends an interval of “at least 7 days”. Participants will not be impeded in taking up an offer of a COVID-19 vaccine. If a participant receives a COVID-19 vaccine during the trial, both the vaccine and date of administration will be requested and recorded in the eCRF.

If the participant receives an adenoviral-based COVID-19 vaccine (or any other adenoviral vaccine) during the trial, the participant will no longer be eligible to continue with the trial.

10 INVESTIGATIONAL PRODUCTS

All participants will receive the interventions as scheduled for their allocated group, as detailed in section 3. The term 'investigational products' applies to either ChAdOx1 NipahB or 0.9% saline placebo in this study.

10.1 ChAdOx1 NipahB

ChAdOx1 NipahB 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 glass vials for intramuscular administration and will be stored at nominal -80°C in a secure freezer at the clinical site.

Batch number NI22A23A (used for this trial) is presented in formulation buffer (10 mM Histidine, 7.5% (w/v) sucrose, 35 mM NaCl, 1 mM MgCl2, 0.1% (w/v) PS80, 0.1 mM Edetate Disodium, 0.5% (v/v) ethanol, pH 6.6). The appearance of ChAdOx1 Nipah is a slightly opaque frozen liquid, essentially free from visible particulates.

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

10.2 Saline Placebo (0.9% Sodium Chloride)

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

10.3 Blinding of IMPs

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

10.4 Storage of ChAdOx1 NipahB

ChAdOx1 NipahB requires storage in a freezer at -70°C to -85°C and will be transported to the study site(s) after authorised release for use in the clinical trial by the CBF Qualified Person (QP) and study approval by REC and MHRA. Movements of study medication between CBF and the study site(s) will be documented in accordance with relevant SOPs.

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 that are able to move the product in the event of significant temperature deviation.

10.5 Compliance with Trial Treatment

The study investigational product and placebo will be administered by trained unblinded study personnel and will be documented according to GCP guidelines and relevant SOPs. Issues related to

compliance are therefore the responsibility of study personnel who have received appropriate training.

10.6 Accountability of The Trial Treatment

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

The vaccine will be delivered and stored at the study site(s) pending authorised release for use in the clinical trial.

10.7 Concomitant Medication

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

10.8 Emergency Medication and Procedures

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

10.9 Post-Trial Treatment

Study IMP will not be continued beyond the trial period.

10.10 Other Treatments (non-IMPs)

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

10.11 Other Interventions

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

11 SAFETY REPORTING

11.1 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death, • Is life-threatening, • Requires inpatient hospitalisation or prolongation of existing 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 Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • In the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product, or • In the case of any other investigational medicinal product, in the approved Investigator's Brochure (IB) relating to the trial in question.

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

Table 5 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 (ADEM)
	Encephalopathy
	Encephalitis / encephalomyelitis
	Aseptic meningitis
	Stroke
Haematological / Vascular	Thrombocytopenia
	Thrombosis with Thrombocytopenia Syndrome (TTS)
	Major thrombosis (without thrombocytopenia)
	Heparin-Induced Thrombocytopenia (HIT)
	Immune thrombocytopenic purpura (ITP)
	Disseminated intravascular coagulation (DIC)
Immunological	Anaphylaxis
	Vasculitis
	Capillary Leak Syndrome (CLS)
	Other Immune-Mediated Conditions
Other	Acute renal failure
	Serious injection site reaction, such as ulceration, abscess or necrosis

11.3 Causality Assessment

The relationship of each adverse event to the trial vaccine or study procedures must be determined by a PI-delegated blinded clinician / Investigator. The relationship of the adverse event with the study procedures will be categorized as not related, possibly related, probably related or definitely related.

The delegated clinician will use clinical judgement to determine the relationship using the following definitions (Table 6):

Table 6 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

As no expected SARs are recorded in the 'Reference Safety Information' (section 5.4 of the ChAdOx1 NipahB Investigator's Brochure), any SARs associated with ChAdOx1 NipahB 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. Laboratory adverse event severity gradings will be used; they are listed in Appendix B: Severity Grading Scales.

11.6 Procedures for Collecting and Recording Adverse Events

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

All AEs that are observed by the Investigator or reported by the participant irrespective of their relatedness to the study vaccination will be recorded from the day of vaccination for 28 days. These will be recorded in either the eDiary (by the participant) and/or eCRF (by blinded study investigators). 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.

11.7 Solicited Adverse Events

Predefined local and systemic solicited AEs for reactogenicity assessment, as listed in Table 7, will be collected in an electronic diary for 7 days (on days 0-6) following administration of the vaccine. Participants will measure and record their temperature and the diameter of any injection site redness with a provided thermometer and tape measure respectively, and AE severity gradings will be classified based on these measurements. For all other solicited AEs, solicited AE severity will be self-assessed by participants according to severity grading scales provided to them as defined in Appendix B: Severity Grading Scales.

Table 7 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 symptoms?” (which are not solicited adverse events on days 0-6 following vaccination and do not constitute SAEs or AESIs) will be collected for 28 days (on days 0-27) following administration of the IMP. These will be recorded in the participant’s eDiary and then recorded by the study team in the relevant eCRF.

11.9 eDiary AEs

11.9.1 eDiary Collection of Solicited Adverse Events

From the time of each vaccine administration up to 7 days post-vaccination (day of vaccination and six subsequent days), solicited adverse events will be recorded by the participant in an electronic diary and graded by the participant. If further action is required following an AE including face-to-face medical review and/or prescribed medication, this will be recorded by the study team in the eCRF. Causality will be assigned by blinded PI-delegated clinician / Investigator. Any solicited AE which meets the definition of a SAE will be managed and reported as per Section 11.15.

11.9.2 eDiary Collection of Unsolicited Adverse Events

From the time of each vaccine administration up to 28 days post-vaccination (day of vaccination and 27 subsequent days), unsolicited adverse events will be collected using the eDiary and reviewed at clinic visits. If a participant records a grade 3 or 4 adverse event, an email alert is sent to the investigator(s), so that the investigator is aware and can review appropriately. 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. These unsolicited adverse events will be recorded in the AE section of the eCRF. Unsolicited adverse events recorded in the eDiary will be severity-graded by the participant. Causality will be assigned by the blinded PI-delegated clinician / Investigator as per section 11.3.

11.10 Observation Related AEs

Physical observations of the patient (e.g. temperature, blood pressure, heart rate) will be taken according to the schedule of procedures. These will be recorded in the eCRF. If abnormal, a severity grading will be assigned by the study team as per Appendix B: Severity Grading Scales.

11.11 Visit Elicited AEs

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

11.12 Laboratory AEs

Severity grading for laboratory AEs are defined in Appendix B: Severity Grading Scales. All changes in laboratory values will be recorded as AEs if they are of Grade 2 severity or above. Changes of laboratory values of Grade 1 severity may be recorded as AEs if they are judged to be clinically significant by a blinded PI-delegated clinician / Investigator.

If a test result is deemed clinically significant, it may be repeated to ensure it is not a single occurrence or spurious result. If a test result remains clinically significant, the participant will be informed and advised with regards to 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.

11.13 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 at which point it would fall within the definition of "serious" and the congenital abnormality of birth defect would be reported as an SAE. Pregnancy notification and follow-up reports on pregnancy outcome will be provided to the DSMC with the ongoing consent of the participant.

11.14 Following Up of AEs

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

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

The CI on behalf of the Sponsor will be responsible for unblinding in the event of serious adverse reactions and will be responsible for the reporting of any SUSARs (as detailed in section 11.17). Any SUSAR must be reported to the DSMC.

Unrelated SAEs will be reported to the DSMC for discussion at the next scheduled DSMC review (11.22.1).

Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form notified by the study team to the CI, who will then notify the DSMC.

The DSMC 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.

11.16 Events Exempt from Reporting as SAEs

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

11.17 SUSAR Reporting

All SUSARs will be reported to the Sponsor, relevant Research Ethics Committee and to the MHRA. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. Any additional relevant information should be sent within 8 days of the report.

The CI or delegate will also inform all Investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

11.18 Development Safety Update Report

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

The Development International Birth Date (DIBD) for ChAdOx1 NipahB is 19th October 2023 and the data lock point of each DSUR will be the last day of each one-year reporting period (18th October).

11.19 Safety Profile Review

The safety profile will undergo blind review on a regular basis by the Investigators using the electronic diary, adverse events eCRF and safety bloods. Any concerns will be referred to the blinded CI. If the CI remains concerned they may consider unblinding and/or escalation to the unblinded DSMC as required.

11.20 Trial Management Group

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

11.21 Data Safety Monitoring Committee (DSMC)

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 NIV001 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.

11.22 Interim Safety Reviews

11.22.1 Sequence of Enrolment and Vaccination

An initial cohort of 6 participants (Cohort 1) will be enrolled and receive their first vaccine prior to the enrolment of further participants. Enrolment will be staggered within Cohort 1 (Table 8). The first participant enrolled into the trial will be vaccinated alone, ahead of any other participants. Their profile of adverse events including day 2 laboratory results will be reviewed for at least 48 hours post-vaccination. Provided there are no safety concerns, as assessed by the PI, a further 2 participants will be vaccinated at least 1 hour apart from each other. The profile of adverse events for the second and third participants, including day 2 laboratory results, will then be reviewed by the PI after a further 48 hours and if deemed acceptable, the remaining 3 participants in the group may then be vaccinated.

Enrolment of the remaining participants in the trial (Cohort 2) will continue only after a positive decision from the DSMC following the first DSMC safety review (detailed in section 11.22.1).

Table 8 Sequence of Enrolment (First Doses)

Sequence	Participant groups	Minimum interval before progressing to next step	Safety review before progression
Step 1	Cohort 1 volunteer 1	48 hours	Local safety review (PI)
Step 2	Cohort 1 volunteer 2	1 hour	Clinical team involved with vaccination
Step 3	Cohort 1 volunteer 3	48 hours	Local safety review (PI)
Step 4	Cohort 1 remaining volunteers	7 days	DSMC review
Step 5	Cohort 2	n/a	n/a

Administration of the second doses of vaccine to participants in Cohort 2 will only occur once participants in Cohort 1 have had their second vaccine doses and after an interim safety review conducted DSMC (detailed in section 11.22.1).

11.22.1 DSMC Reviews

DSMC data reviews will be done as follows:

1. Formal review of the safety profile data after 7 days following the first vaccination of all 6 participants in Cohort 1. This review will decide on progression to administering the first dose of vaccine to the remaining participants (Cohort 2) in the trial.
2. Formal review of the immunological and safety profile including data up to 28 days after the first dose of vaccine has been administered to all participants in Cohort 1 and the first 18

participants in Cohort 2 (total 24 participants). The trial will continue in parallel to this DSMC review.

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

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

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

11.23 Procedures to be Followed in the Event of Abnormal Findings

Laboratory parameters for inclusion/exclusion in the trial will be considered on an individual basis, with investigator discretion for interpretation of results and the need for repeated tests. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. If a test result 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 medical care arranged as appropriate and 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.

11.24 Safety Holding Rules

11.24.1 Group Holding Rules

The group holding rules are as follows:

- **Solicited local adverse events**:
    - If 2 or more participants (per dose of vaccination) experience the same grade 3 solicited local adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at grade 3 for >48 hrs.

- **Solicited systemic adverse events**:
    - If 2 or more participants (per dose of vaccination) experience the same grade 3 solicited systemic adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at grade 3 for >48 hrs.

- **Unsolicited adverse events**:

- If 2 or more participants (per dose of vaccination) experience the same grade 3 unsolicited adverse event (including the same laboratory adverse event, excluding lymphopenia) 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, the CI on behalf of the Sponsor will inform the regulatory authority. The DSMC will be asked to review relevant safety data and provide a recommendation on further dosing. If the DSMC recommend to restart dosing, the request (with pertinent data) must be approved by the regulatory authority prior to restarting dosing. The DSMC review would consider:

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

The vaccine manufacturer (CBF) will also be notified if a holding rule is activated or released. All vaccinated 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.

11.24.2 Individual Holding Rules

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

- **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 (day of vaccination and one subsequent day) and persisting at Grade 3 for >48hrs.
- **Laboratory AEs**: the participant develops a Grade 3 laboratory adverse event (excluding lymphopenia) considered possibly, probably or definitely related to vaccination within 7 days after vaccination and persisting at Grade 3 for >48hrs (laboratory AE reference ranges are included in Appendix B: Severity Grading Scales).
- **Unsolicited adverse events**:

- The participant has a Grade 3 adverse event considered possibly, probably or definitely related to vaccination, persisting continuously 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 participant 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.

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 (eCRF) using a REDCap database. The database will be stored on a secure University of Oxford server and will have restricted access (password-protection) and accountability records. These data include safety data, laboratory data (both clinical and immunological) and outcome data. All information transcribed to and from the database will be done by encrypted (Https) transfer.

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

12.1 Data Integrity

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

12.2 Data Archiving and Storage

Study data will be stored electronically on a secure server, and paper notes will be kept in a secure location at the study site(s). All essential documents, which includes research data and identifiable information, will be retained for a minimum of 5 years after the study has finished. 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 de-identified research data securely at the site

at least 99 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. Volunteers who complete online screening or telephone screening only (before informed consent) will not have data kept beyond the end of the trial.

12.3 Source Data

Source documents are original documents, data, and records from which participants' eCRF 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 eCRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. In this study, eCRF entries will be considered source data where it is the site of the original recording. All documents will be stored safely under strict confidentiality and with restricted access. On all study-specific documents, other than the signed consent and the participant contact sheet, the participant will be referred to by the study participant number/code only.

12.4 Access to Data

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

12.5 Data Recording and Record Keeping

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

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

personal information and medical information including blood test results may be accessed to avoid unnecessary repetition. If participants provide specific consent, we will use personal identifiable data to invite participants for future research.

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 calculations, or presentation of p-values for group comparisons.

Counts and percentages of local and systemic solicited adverse reactions from eDiaries during days 0-6 following each vaccination will be presented for each group. Unsolicited AEs occurring during days 0-27 following each vaccination, and all SAEs and AESIs occurring throughout the duration of the study will be summarised.

Highly skewed antibody and cellular response data will be log-transformed prior to analysis. The geometric mean titres (GMTs) and associated 95% confidence intervals (CIs) will be summarised by computing the anti-log of the mean of the log-transformed data. Medians and interquartile ranges of the untransformed data may additionally be presented.

Due to the descriptive nature of the trial, no testing will be performed between groups.

13.1.2 The Number of Participants

Fifty-one participants will be enrolled into the study, allocated to Cohorts 1 or 2. Participants are only considered enrolled once they receive the first dose of vaccine. Recruitment will continue until fifty-one participants are enrolled.

There has been no power calculation to determine these numbers, as the study is descriptive. The sample size was chosen in line with the primary objective of providing adequate descriptive safety information to permit further evaluation in larger clinical trials. A total of 20 participants per vaccine schedule (groups 1 and 2) was deemed sufficient for a first-in-human phase I trial. With 46 participants receiving at least one dose of ChAdOx1 NipahB vaccine, the probability of observing at least one participant with an adverse event will be more than 90% if the underlying incident rate is 5%.

13.1.3 The Level of Statistical Significance

Any statistical significance testing will not be testing any hypotheses, but will be purely descriptive and hypothesis generating. All confidence intervals for descriptive analyses will be set at 95%.

13.1.4 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 of this occurring.

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

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

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

13.1.6 Inclusion in Analysis

All enrolled participants with any available data will be included in the analyses. All analyses will be 'as treated'.

13.1.7 Interim Analysis

An interim analysis of safety outcomes will occur at the interim safety reviews as described in section 11.22. Interim safety and immunogenicity analyses are scheduled following the 4-week timepoint after the first vaccination, as detailed in section 11.22.1. The purpose of these analyses are to inform future planning and manufacture only. The results of the interim analyses will have no bearing on the remaining conduct of the study, and will therefore not compromise the integrity of the trial. The validity of the final analyses will not be affected. When performed on a subset of the trial population, the analysis will be undertaken with the caveat that the results and conclusions are subject to change once data from all participants has been analysed.

14 ETHICS AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

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

14.2 Guidelines for Good Clinical Practice

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

14.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet, and required material will be submitted to an appropriate Research Ethics Committee (REC), HRA (if relevant), regulatory authorities (MHRA in the UK), and host 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 ISRCTN 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 organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and summary report will be submitted to the MHRA, the REC, host organisation and Sponsor.

14.6 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. Participants will be identified only by a participant ID number on all trial documents and any electronic database (except for the participant electronic diaries where an email address will also be used). 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.

Tests for Hepatitis B and C are carried out as part of the screening investigations for this trial. Hepatitis B and C are notifiable organisms listed under the UK Health Protection (Notification) Regulations 2010 and therefore must be reported to the relevant public health authority if they are suspected. Notification of infectious diseases is mandatory under UK law and participants will not be able to opt out of reporting. This will be included in the participant information sheet.

14.7 Participant Financial Compensation

Participants will be reimbursed £110 for their screening visit and each vaccination visit. For each of the follow up visits, participants will be reimbursed £90. Upon completion of each diary card participants will be reimbursed a further £30.

Each participant can therefore receive a maximum of:

- The first six participants; cohort 1: £1,380
- The remaining 45 participants; cohort 2: £1020

An additional £90 reimbursement will be provided for any unscheduled visit(s). 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.

Participants will be reimbursed *pro rata* at scheduled timepoints during the study:

- The first six participants; cohort 1: Following visits 1, 4, 7 and 13
- The remaining 45 participants; cohort 2: Following visits 1, 5 and 9

Participants who attend screening but are not enrolled in the study (i.e., do not complete any further study visits) will be reimbursed following their screening visit. If a participant withdraws consent for continued participation in the trial or is withdrawn for any other reason, they will be compensated for any trial visits they attended.

15 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

15.1 Investigator procedures

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

15.2 Risk Assessment

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

15.3 Monitoring

Monitoring will be performed according to GCP by OVG. Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Trial site(s) 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 QA at OVG manager conducts systems-based internal audits to check that trials are being conducted according to local procedures and in compliance with GCP and applicable regulations.

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

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

16 FINANCING AND INSURANCE

16.1 Financing

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

16.2 Insurance

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

16.3 Contractual Arrangements

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

17 SERIOUS BREACHES

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

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

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

(b) the scientific value of the trial”.

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

18 PUBLICATION POLICY

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

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

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

20 ABBREVIATIONS

Abbreviations	
ADEM	Acute Disseminated Encephalomyelitis
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
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
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic acid
DSMC	Data Safety Monitoring Commitee
DSUR	Development Safety Update Report
EBV	Epstein Barr virus
EBOD	Ebola Virus Disease
EBOV	Zaire Ebolavirus
EDC	Electronic Data Capture
ELISA	Enzyme linked immunosorbent assay
ELISpot	Enzyme linked immunospot assay
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ePRO	Electronic participant reported outcomes
FDA	Food and Drug Administration
Filovirus GP	Filovirus Glycoprotein
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GMO	Genetically modified organism
GMP	Good Manufacturing Practice
GP	General Practitioner
HBsAg	Hepatitis B surface antigen
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HEK	Human embryonic kidney
HIT	Heparin-Induced Thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority

Abbreviations	
IB	Investigators Brochure
ICH	International Conference on Harmonisation
ICS	Intracellular Cytokine Staining
IFN	Interferon
IM	Intramuscular/intramuscularly
IMP	Investigational medicinal product
ISF	Investigator Site File
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
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
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NiV	Nipah virus
NiV_B	Nipah virus Bangladesh strain
NiV_M	Nipah virus Malaysia strain
OUHFT	Oxford University Hospital Foundation Trust
OVC	Oxford Vaccine Centre
OVG	Oxford Vaccine Group
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase Chain Reaction
PEP	Post-exposure prophylaxis
PFU	Pore forming units
PIC	Participant Identification Centres
PIS	Participant information sheet
PrEP	Pre-exposure prophylaxis
PT	Preferred terms
QP	Qualified Person
RCT	Randomised controlled trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance (formerly Clinical Trials and Research Governance)
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SFU	Spot forming units

Abbreviations	
SmPC	Summary of Product Characteristics
SOC	System Organ Classes
SOP	Standard Operating Procedure
SUDV	Sudan Ebolavirus
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TOPS	The Over-Volunteering Prevention System
TTS	Thrombosis with thrombocytopenia
UKHSA	United Kingdom Health Security Agency
VAERS	Vaccine Adverse Event Reporting System
VNA	Virus neutralising assay
vp	Viral particles
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

21 REFERENCES

1. World Health Organization. Prioritizing diseases for research and development in emergency contexts. Prioritizing diseases for research and development in emergency contexts (accessed 15 September 2022).

2. National Institute of Allergy and Infectious Diseases. NIAID Emerging Infectious Diseases/Pathogens. 2018. https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens2022).

3. United Kingdom Health Security Agency. High consequence infectious diseases (HCID). 2018. https://www.gov.uk/guidance/high-consequence-infectious-diseases-hcid (accessed 15 September 2022).

4. Lam SK, Chua KB. Nipah virus encephalitis outbreak in Malaysia. *Clin Infect Dis* 2002; **34 Suppl 2**: S48-51.

5. Chua KB, Bellini WJ, Rota PA, et al. Nipah Virus: A Recently Emergent Deadly Paramyxovirus. *Science* 2000; **288**(5470): 1432-5.

6. World Health Organization. Nipha research and development (R&D) roadmap. 2019. https://cdn.who.int/media/docs/default-source/blue-print/nipah_rdblueprint_roadmap_advanceddraftoct2019.pdf?sfvrsn=4f0dc9ad_3&download=true.

7. Arunkumar G, Chandni R, Mourya DT, et al. Outbreak Investigation of Nipah Virus Disease in Kerala, India, 2018. *The Journal of Infectious Diseases* 2019; **219**(12): 1867-78.

8. Ching PK, de los Reyes VC, Sucaldito MN, et al. Outbreak of henipavirus infection, Philippines, 2014. *Emerg Infect Dis* 2015; **21**(2): 328-31.

9. Ambat AS, Zubair SM, Prasad N, et al. Nipah virus: A review on epidemiological characteristics and outbreaks to inform public health decision making. *Journal of Infection and Public Health* 2019; **12**(5): 634-9.

10. Khusro A, Aarti C, Pliego AB, Cipriano-Salazar M. Hendra Virus Infection in Horses: A Review on Emerging Mystery Paramyxovirus. *Journal of Equine Veterinary Science* 2020; **91**: 103149.

11. Harcourt B, Lowe L, Tamin A, et al. Genetic Characterization of Nipah Virus, Bangladesh, 2004. *Emerging Infectious Disease journal* 2005; **11**(10): 1594.

12. Bossart KN, Tachedjian M, McEachern JA, et al. Functional studies of host-specific ephrin-B ligands as Henipavirus receptors. *Virology* 2008; **372**(2): 357-71.

13. Bossart KN, Crameri G, Dimitrov AS, et al. Receptor binding, fusion inhibition, and induction of cross-reactive neutralizing antibodies by a soluble G glycoprotein of Hendra virus. *J Virol* 2005; **79**(11): 6690-702.

14. Halpin K, Hyatt AD, Fogarty R, et al. Pteropid Bats are Confirmed as the Reservoir Hosts of Henipaviruses: A Comprehensive Experimental Study of Virus Transmission. *The American Society of Tropical Medicine and Hygiene* 2011; **85**(5): 946-51.

15. Singh RK, Dhama K, Chakraborty S, et al. Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies - a comprehensive review. *Vet Q* 2019; **39**(1): 26-55.

16. Rahman MA, Hossain MJ, Sultana S, et al. Date Palm Sap Linked to Nipah Virus Outbreak in Bangladesh, 2008. *Vector-Borne and Zoonotic Diseases* 2011; **12**(1): 65-72.

17. Luby SP, Rahman M, Hossain MJ, et al. Foodborne Transmission of Nipah Virus, Bangladesh. *Emerging Infectious Disease journal* 2006; **12**(12): 1888.

18. Gurley ES, Montgomery JM, Hossain MJ, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. *Emerg Infect Dis* 2007; **13**(7): 1031-7.

19. Islam MS, Sazzad HM, Satter SM, et al. Nipah Virus Transmission from Bats to Humans Associated with Drinking Traditional Liquor Made from Date Palm Sap, Bangladesh, 2011-2014. *Emerg Infect Dis* 2016; **22**(4): 664-70.

20. Lo MK, Rota PA. The emergence of Nipah virus, a highly pathogenic paramyxovirus. *Journal of Clinical Virology* 2008; **43**(4): 396-400.

21. Hossain MJ, Gurley ES, Montgomery JM, et al. Clinical Presentation of Nipah Virus Infection in Bangladesh. *Clinical Infectious Diseases* 2008; **46**(7): 977-84.

22. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; **396**(10249): 467-78.

23. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *The Lancet* 2020; **396**(10267): 1979-93.

24. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet* 2021; **397**(10269): 99-111.

25. Voysey M, Clemens SAC, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *The Lancet* 2021; **397**(10277): 881-91.

26. van Doremalen N, Lambe T, Sebastian S, et al. A single-dose ChAdOx1-vectored vaccine provides complete protection against Nipah Bangladesh and Malaysia in Syrian golden hamsters. *PLOS Neglected Tropical Diseases* 2019; **13**(6): e0007462.

27. van Doremalen N, Avanzato VA, Goldin K, et al. ChAdOx1 NiV vaccination protects against lethal Nipah Bangladesh virus infection in African green monkeys. *npj Vaccines* 2022; **7**(1): 171.

28. Gómez Román R, Tornieporth N, Cherian NG, et al. Medical countermeasures against henipaviruses: a review and public health perspective. *The Lancet Infectious Diseases* 2022; **22**(1): e13-e27.

29. Monath TP, Nichols R, Tussey L, et al. Recombinant vesicular stomatitis vaccine against Nipah virus has a favorable safety profile: Model for assessment of live vaccines with neurotropic potential. *PLoS Pathog* 2022; **18**(6): e1010658.

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

31. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet (London, England)* 2020; **396**(10249): 467-8.

32. Antrobus RD, Coughlan L, Berthoud TK, et al. Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. *Molecular therapy : the journal of the American Society of Gene Therapy* 2014; **22**(3): 668-74.

33. Coughlan L, Sridhar S, Payne R, et al. Heterologous Two-Dose Vaccination with Simian Adenovirus and Poxvirus Vectors Elicits Long-Lasting Cellular Immunity to Influenza Virus A in Healthy Adults. *EBioMedicine* 2018.

34. World Health Organization. WHO guidelines on non-clinical evaluation of vaccines, Annex 1, TRS No 927. 2005. https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccines-annex-1-trs-no-927.

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

36. Barrett JR, Belij-Rammerstorfer S, Dold C, et al. Phase 1/2 trial of SARS-CoV-2 vaccine ChAdOx1 nCoV-19 with a booster dose induces multifunctional antibody responses. *Nat Med* 2021; **27**(2): 279-88.

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:**
Professor Brian Angus		31/10/2024

Lead Statistician 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:

Lead Statistician	**Signature:**	**Date:**
Natalie Marchevsky		30/10/2024

Principal 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:

Principal Investigator	**Signature:**	**Date:**
Professor Brian Angus		31/10/2024

23 Appendix B: Severity Grading Scales

Table 9 Severity grading criteria for local adverse events *erythema ≤2.5cm is an expected consequence of skin puncture and will therefore not be considered an adverse event

Adverse Event	Grade	Intensity
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis

Table 10 Severity grading criteria for local and systemic AEs. NB: A&E assessment in itself does not constitute a SAE. Refer to 11.1 for SAE definitions.

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
GRADE 2	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
GRADE 4	Potentially Life-threatening: requires assessment in A&E or hospitalisation

Table 11 Severity grading criteria for physical observations (applies to adults only). *Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
Fever (oral)	38.0°C - 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C	> 40°C

Tachycardia (bpm)*	101 - 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalisation for malignant hypertension
Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalisation for malignant hypertension
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80	A&E visit or hospitalisation for hypotensive shock
Respiratory Rate (breaths per minute)	17 - 20	21-25	>25	Intubation

Table 12 Oxford Vaccine Group Site Specific Severity Grading Scale for Laboratory AEs

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

24 Appendix C: Document History

Version	Author	Changes
1.0	Ilsa Haeusler, Daniel Jenkin	Document created
2.0	Daniel Jenkin	Response to MHRA notice of non-acceptance: • Section 4.3, 6.1, 14.7: Addition of D1 and V2+1 visits to increase in-person safety assessments for cohort 2. Updated schedule of procedures and outcomes tables to reflect this (re: clinical GNA point 1). Consequent update to participant compensation • Section 4.2, 4.3: Addition of pregnancy test at the final study visit (re: clinical GNA point 2) • Sections 4.1, 4.2, 4.3, 9.4.1: Clarification that – in keeping with the CTRG contraception guidance – only a "highly sensitive" urinary pregnancy test may be used to confirm absence of pregnancy (re: clinical GNA point 3) • Section 8.1.2: Maximum alcohol intake exclusion criteria reduced to 14 units per week (re: clinical GNA point 4) • Section 8.4: Correction of oophorectomy spelling (re: Clinical remark A) Response to initial REC review: • Section 14.6 Confidentiality: Paragraph added detailing mandatory notification of infectious diseases (due to hepatitis B and C screening tests carried out for the trial)
3.0	Daniel Jenkin, Ella Morey	Updates included in Substantial Amendment 1: • Section 9.2.1: Clarification surrounding the accessing of participants medical records following online/in person consent • Section 10.4: Storage temperature range of ChAdOx1 NipahB updated to align with IMPD • Section 11.18: Development International Birth Date (DIBD) for ChAdOx1 NipahB and data lock point of each DSUR added. • Section 22, Appendix A: Lead Statistician updated from Dr Xinxue Liu to Natalie Marchevsky

4.0	Thejaswini Madupuri	Updates included in Substantial Amendment 2: • Change of Chief Investigator from Professor Sir Andrew Pollard to Professor Brian Angus