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

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

Study Code: NIV002

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University of Oxford team:

Chief Investigator: Prof Brian Angus

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Research Protocol Number: PR-25005

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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 trial 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 which causes COVID-19. Preliminary data from the first-in-human phase 1 trial of ChAdOx1 NipahB in Oxford, UK, supports the safety and immunogenicity of the vaccine. The purpose of this trial is to assess the safety and immune response of the ChAdOx1 NipahB in Bangladeshi adults. The vaccine is being evaluated as both a single dose and a two-dose regimen in this trial. The vaccine developer aims to develop a single dose for quick protection during outbreaks, while two doses are intended to provide longer-term protection, such as for healthcare workers in affected regions.

We will recruit 306 healthy people aged 18 to 55 years. Participants will first be checked for eligibility with an in-person medical assessment. The first 6 eligible participants will all be assigned to receive two doses of the ChAdOx1 NipahB vaccine and will not be blinded. After these, the remaining 300 participants will each be randomly assigned by a computer to one of three different groups. Group 2A will receive two doses of the ChAdOx1 NipahB vaccine, group 2B will receive one dose of the ChAdOx1 NipahB vaccine followed by one dose of sterile salt water, and group 2C will receive one dose of an approved vaccine for an unrelated condition (an inactivated polio vaccine) followed by one dose of sterile salt water. The intramuscular injections will be given 12 weeks apart. The study team and vaccine participants will be blinded to the vaccines they have received until the end of the study. Participants will be followed up for 1 year from the first vaccination.

3 SYNOPSIS

Country	Bangladesh
Trial code	NIV002
Internal Reference Number	OVG2024/04
Trial Site	icddr,b
Sponsor	University of Oxford
Clinical phase	IIa
Study Design	Single site, double blind, randomised controlled trial with an open label non-randomised lead-in cohort
Population	Healthy non-pregnant adults aged 18 to 55
Planned Sample Size	N=306 (lead-in cohort n=6, main cohort n=300)
Follow-up duration	12 months (from first dose)
Primary Immunogenicity Objective	To assess the immunogenicity of ChAdOx1 NipahB in a one and two-dose schedule in adults, by measurement of ELISA responses to Nipah glycoprotein G at 28 days post each dose
Primary Safety Objective	To assess the safety profile of ChAdOx1 NipahB in adult volunteers
Secondary Objectives	To assess the kinetics and durability of antibody responses to Nipah glycoprotein G using a one and two-dose schedule of ChAdOx1 NipahB
Investigational Products	1. SIIPL Manufactured ChAdOx1 NipahB (5×10^{10} vp per dose) 2. Comparator: Inactivated Polio Vaccine (dose 1) and saline placebo (dose 2)
Route	Intramuscularly (IM) into the deltoid region of the arm

Lead-in cohort: (open label, sentinel cohort)

Cohort	Group	Number of participants	Intervention 1	Intervention 2
			(Week 0)	(Week 12)
1	A	6	ChAdOx1 NipahB	ChAdOx1 NipahB

Main cohort: (5:5:2 randomised, participant-observer blinded)

Cohort	Group	Number of participants	Intervention 1	Intervention 2
			Week 0	Week 12
2	1	125	ChAdOx1 NipahB	ChAdOx1 NipahB
	2	125	ChAdOx1 NipahB	Saline placebo
	3	50	Inactivated Polio Vaccine	Saline placebo

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	X
Vital signs (heart rate, temperature, blood pressure) and height and weight	X
Screening physical examination	X
Urine Samples	
Urinary hCG (WOCBP only)[2]	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]WOCBP: women of childbearing potential

[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)

4.2 Schedule of Procedures Table: Vaccination and Follow up Visits

Table 2 Schedule of Procedures Table: Vaccination and Follow up Visits

Visit type	Vac 1	Daily community visits	f/u	f/u	f/u	Vac 2	Daily community visits	f/u	f/u	f/u	f/u
Timeline[1]	D0	D0-6	D7	D14	D28	Vac2 (D84)	Vac2+(0-6)	Vac2 +7	Vac2 +14	Vac2 +28	Vac2 +281
Time window (days)		±0	-0/+3	±3	±3	±14	±0	-0/+3	±3	±3	±60
Visit Procedures											
Review contraindications, inclusion and exclusion criteria	x					x					
Randomisation	x										
Vaccination	x					x					
Vital signs (heart rate, blood pressure)	x		x	x	x	x		x	x	x	
Temperature	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)
Adverse Event Collection											
Solicited AE collection (7 days)	x	x				x	x				
Unsolicited AE collection (28 days)	x	x	x	x	x	x	x	x	x	x	
SAEs & AESI collection	x	x	x	x	x	x	x	x	x	x	x
Review ongoing AEs		x	x	x	x	x	x	x	x	x	x
Urine Samples											
Urinary hCG (WOCBP only)[2]	x					x					
Blood Samples[3]	*					*					
Biochemistry, Haematology (mL) [LFTs, U+Es, FBC]	~3	-	~3	~3	~3	~3	-	~3	~3	~3	-
Immunology (mL)	~7	-	~7	~7	~12	~7	-	~7	~12	~7	~10
Blood volume per visit (mL)	~10	-	~10	~10	~15	~10	-	~10	~15	~10	~10
Cumulative blood volume (mL)	~20	-	~30	~40	~55	~65	-	~75	~90	~100	~110

f/u = clinic visit

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

[2]WOCBP: women of child bearing potential. [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)

*Blood samples drawn prior to vaccination

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] and almost annually in Bangladesh. The case fatality rates from these outbreaks are between 75-100%. Up to 2024, there have been an estimated 742 human cases diagnosed and reported (265 from Malaysia, 343 Bangladesh, 107 from India, 17 from the Philippines, and 11 from Singapore).[8,9]

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 seems 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.[21,22] 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.

Nipah virus poses a serious public health challenge to Bangladesh, where outbreaks are reported on a near annual basis. Conducting this phase IIa Nipah vaccine trial in Bangladesh enables assessment

of the vaccine in a key Nipah-affected country, where a successfully developed Nipah vaccine could be deployed in the future. Partnering with icddr,b, which has a strong background in clinical vaccine research and an active Nipah virus research program, will also provide the expertise and infrastructure necessary to effectively conduct this study.

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[23-26] 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 in 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 Table 3).

5.3.2 ChAdOx1 NipahB Non-Clinical Studies

Non-clinical studies are described within the ChAdOx1 NipahB Investigator's Brochure. In brief, the vaccine has been shown to be immunogenic and protective against Nipah challenge in African green monkeys and Syrian golden hamsters and the vaccine was well tolerated in a repeat dose GLP toxicology study in balb/c mice.

5.3.3 ChAdOx1 NipahB Clinical Studies

Clinical evaluation of ChAdOx1 NipahB began with NIV001 (ISRCTN87634044), a phase I first-in-human clinical trial carried out in Oxford, UK. NIV001 trial began on 5th January 2024 and remains ongoing. The trial consists of an open label sentinel cohort (cohort 1) of 6 volunteers who received two doses of ChAdOx1 NipahB. The main cohort of the trial (cohort 2) is observer-participant blinded and consists of 45 participants who were 4:4:1 randomised to either a single dose ChAdOx1 NipahB plus saline (n=20), two doses of ChAdOx1 NipahB (n=20) or two doses of saline (n=5). Full recruitment of the

sentinel (6/6) and main cohorts (45/45) has occurred. All sentinel participants and 44/45 main cohort participants received both doses, with one main cohort volunteer withdrawing before the second dose (unrelated to IMP administration).

NIV001 has undergone four DSMB reviews without any safety concerns or activation of holding rules. No serious adverse events have occurred, and solicited adverse events were mostly mild to moderate, with 3/45 participants short-lived severe graded. Three grade 3 lymphopenias, assessed as related to study treatment, were brief, and thrombocytopenia was identified in two asymptomatic volunteers but attributed to pre-existing conditions or spurious results. Preliminary immunogenicity data from cohort 1 (n=6) indicates the vaccine is immunogenic, inducing antibodies to both Nipah Bangladesh and Malaysia strain glycoprotein G after a single dose. A second dose provided further boosting, achieving detectable neutralizing antibodies in all sentinel participants.

Immunological analyses for remaining outcomes and timepoints are pending study completion. Further details of NIV001 are contained within the ChAdOx1 NipahB Investigator's Brochure.

5.4 Other NiV Vaccines in Clinical Testing

The International Clinical Trials Registry Platform was searched on 3rd Sep 2024 for "Nipah". Three other experimental Nipah vaccines in phase I clinical trials were identified. These are summarised in Table 3 Other Nipah Vaccines in Registered Clinical Trials (3rd Sep 2024). Each of the three vaccines in previously registered trials use a different vaccine technology. Apart from ChAdOx1 NipahB, there are no adenoviral-vectored Nipah virus vaccines currently in clinical trials. As yet, there are no published clinical data for these other Nipah virus vaccines.

Table 3 Other Nipah Vaccines in Registered Clinical Trials (3rd Sep 2024)

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 registry status: active, not recruiting)
Live recombinant vesicular stomatitis virus vector vaccine	PHV02	Public Health Vaccines LLC	Phase 1	NCT05178901, 2021	Not available (trial registry status: completed)
			Phase 1	NCT06221813, 2024	Not available (trial registry status: recruiting)
Recombinant subunit vaccine	HeV-sG-V	Auro Vaccines LLC	Phase 1	NCT04199169, 2019	Not available (trial registry status: completed)

5.5 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.[24-28] According to the People's Republic of Bangladesh Directorate General of Health Services (DGHS) data, 56 million doses of the vaccine were administered in Bangladesh with 21 million given as a first COVID-19 vaccine dose, 20 million as a second dose and 16 million as a third dose.[29] DGHS data show the vaccine was administered in Bangladesh from January 2021 until January 2023, with no further doses administered after this period.[29]

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.[30,31] Further details of other ChAdOx1 clinical studies are contained within the ChAdOx1 NipahB Investigator Brochure.

5.6 Rationale for Selected Doses

The regimen and dose planned for this trial were initially evaluated in the ongoing UK first-in-human NIV001 clinical trial. Preliminary data from that trial supports the continued evaluation of the ChAdOx1 NipahB at the 5 x 10^{10} viral particles dose in a one and two dose schedule. The ChAdOx1 NipahB development plan aims to develop the vaccine for use in two different schedules, for two separate indications. These are for a single dose to be used for reactive outbreak use where rapid onset short-to-medium term protection is the priority, and for two doses to be used in a non-outbreak preventative context where longer term protection for high-risk groups is the priority e.g. healthcare workers in at-risk regions and Nipah surveillance teams.

The regimen and dose of ChAdOx1 NipahB (5 x 10^{10} viral particles per dose, as either a single or two-dose administration) was originally selected on the basis of pre-clinical and clinical experience with other ChAdOx1 vaccines. ChAdOx1 nCoV-19 (Vaxzevria/Covishield) 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.[32] 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.[24,33,34] Real-world studies have demonstrated efficacy of ChAdOx1 nCoV-19 following both a single and two-dose regimen.

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, Chikungunya, 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.

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.

5.7 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.

5.7.1 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.

As yet there are no data on the use of ChAdOx1 NipahB in pregnancy, pregnant women will be excluded from the trial and women of childbearing potential will be required to use effective contraception to take part (section 8.5).

Nipah virus human seroprevalence is thought to be low in Bangladesh. A serological study of Nipah virus patient contacts in Bangladesh found that no asymptomatic contacts were positive for Nipah virus IgG.[35]

5.7.2 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.

The approved inactivated polio vaccine being used as a control vaccine in this trial is widely used and has a well-established safety profile which primarily consists short-lived local and systemic reactions within the first 3 days following vaccination. As with any vaccine, there is a very remote chance of a severe allergic reaction or other severe reaction occurring.

5.8 Potential Benefits to Participants

The recruitment population are not expected to benefit directly from the ChAdOx1 NipahB vaccine in this study due to the low risk of Nipah virus infection in Dhaka. 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. Recipients of the inactivated polio vaccine will receive a dose of an approved polio vaccine. If the participant is found to have any medical condition or infection, the investigator will ensure that the participant is provided with appropriate and adequate care or referrals to care in line with good local medical practice. It is hoped that participation in this study will contribute to development and eventual deployment of a Nipah Virus Vaccine to address a global public health concern.

6 OBJECTIVES AND ENDPOINTS

6.1 Objectives, Outcome Measures and Evaluation Timepoints

Outcome	Objective	Outcome measure	Evaluation timepoints[1]
Primary Immunogenicity	To assess the immunogenicity of ChAdOx1 NipahB in a one and two-dose schedule in adults, by measurement of ELISA responses to Nipah glycoprotein G at 28 days post each dose	NipahB glycoprotein G-specific serological response as measured by ELISA	D0, D28, V2, V2+28
Primary Safety	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)	D0 to D28; V2 to V2+28
		d) Occurrence of abnormal safety laboratory measures	D0, D7, D14, D28, V2, V2+7, 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 kinetics and durability of antibody responses to Nipah glycoprotein G in a one and two-dose schedule of ChAdOx1 NipahB	NipahB glycoprotein G-specific serological response as measured by ELISA	D0, D7, D14, D28, V2, V2+7, V2+14, V2+28, V2+281
Exploratory[2]	Exploratory Immunological profiling	Exploratory immunology outcomes may include: • NipahB pseudovirus neutralisation assays • Binding and/or neutralising antibody responses against ChAdOx1 • Further exploratory assays/analyses may be carried out (see section 9.6.2)	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; Further exploratory assays/analyses may be carried out (see section 9.7.2).

7 TRIAL DESIGN

This is a single-site participant-observer blind, randomised, placebo-controlled, phase IIa trial to assess the safety, tolerability and immunogenicity of one or two dose doses of intramuscular (IM) ChAdOx1 NipahB vaccine in healthy adults aged 18 to 55 years in Bangladesh. The trial will be carried out in the clinical trial unit (CTU) of icddr,b in Dhaka.

The first six participants will be non-randomly enrolled into the initial lead-in cohort (Cohort 1). They will receive two doses of ChAdOx1 NipahB, 12 weeks apart. The rationale for the inclusion of this sentinel cohort into this trial, which is the second clinical trial of ChAdOx1 NipahB, is this is the use of the vaccine in this new population (Adults recruited in Bangladesh) and due to a change in manufacturer for this batch of vaccine (Serum Institute of India). Safety evaluations for this group are listed within the schedule of procedures table and include collection of adverse events and clinical laboratory tests.

Following a safety review (at least 7 days after) administration of the first dose to Cohort 1, all remaining participants will be 5:5:2 randomised to the main cohort (Cohort 2) study groups. These consist of

- Group 2A (two doses of ChAdOx1 NipahB, 12 weeks apart)
- Group 2B (single dose ChAdOx1 NipahB, followed by saline at 12 weeks)
- Group 2C the comparator arm (Inactivated Polio Vaccine followed by saline at 12 weeks)

7.1 Study Groups

Lead-in cohort: (open label, sentinel cohort)

Cohort	Group	Number of participants	Intervention 1	Intervention 2
			(Week 0)	(Week 12)
1	1A	6	ChAdOx1 NipahB	ChAdOx1 NipahB

Main cohort: (5:5:2 randomised, participant-observer blinded)

Cohort	Group	Number of participants	Intervention 1	Intervention 2
			Week 0	Week 12
2	2A	125	ChAdOx1 NipahB	ChAdOx1 NipahB
	2B	125	ChAdOx1 NipahB	Saline placebo
	2C	50	Inactivated Polio Vaccine	Saline placebo

7.2 End of Trial Definition

The end of the trial will be complete 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 vaccination for each volunteer. Participants will be considered enrolled in the trial once they have been randomised (or for cohort 1 after receipt of the first vaccination).

8 PARTICIPANT IDENTIFICATION

8.1 Trial Participants

Healthy participants, 18-55 years of age

8.2 Inclusion and exclusion criteria

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

8.2.1 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.
4. Willing and able to give informed consent for participation in the study.
5. Agreement to refrain from blood donation during the course of the study.
6. *For women of childbearing potential only* (as defined by protocol section 8.5)*:* 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.

8.2.2 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 enrolment, or are planning to do so within the trial period.

2. Previous immunisation with an investigational Nipah vaccine.
3. Reported or documented history of previous confirmed or suspected Nipah infection.
4. Administration of immunoglobulins and/or any blood products within three months preceding the planned administration of the vaccine candidate.
5. 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).
6. History of anaphylaxis in relation to vaccination.
7. 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).
8. History of hereditary angioedema, acquired angioedema, or idiopathic angioedema.
9. History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
10. History of any serious psychiatric condition likely to affect participation in the study.
11. *For women only:* participants who are pregnant, breastfeeding or lactating, or are planning pregnancy during the course of the study.
12. 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.
13. 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.
14. History of capillary leak syndrome.
15. 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)
16. Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units per week.
17. Suspected or known injecting drug use within the 5 years preceding enrolment.
18. Detectable circulating hepatitis B surface antigen (HBsAg).
19. Seropositive for hepatitis C virus (antibodies to HCV).
20. 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.
21. 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 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.

8.4 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. Pregnancy

8.5 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.

A woman is considered of childbearing potential after the onset of menarche and until becoming post-menopausal (defined as aged 50 years and above with 12 months of amenorrhoea) unless permanently sterile. A woman is considered permanently sterile if she has undergone any of the following procedures:

- Hysterectomy
- Bilateral salpingectomy
- Bilateral oophorectomy.

Contraception should be maintained for one month prior to receiving the first dose of vaccine and for three months following the final vaccine dose. Female participants of childbearing potential who are

not currently using contraception and wish to participate in the study will be informed by the trial team about the contraceptive requirements for eligibility. Acceptable forms of effective contraception for participants of childbearing 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.

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

The study will be conducted at the clinical trial unit (CTU) of icddr,b in Dhaka. The population for enrolment will be selected from adjoining areas in Mohakhali, Dhaka - Kunipra, Arjat Para, Nakhalpara, Korail, Begunbari, Chairman Bari and Badda – including from informal settlements and more developed areas. The population in these areas is ~300,000, and is a stable population with literacy around 50% and medium-low socio-economic conditions. The area is covered within 1 km of icddr, b CTU.

Study staff will identify eligible persons to be study participants through house-to-house visits in the proposed catchment areas around the CTU sites. Study staff will describe the study and briefly explain the study procedures. Individuals that express an interest to participate in the trial will be invited to attend at CTU, icddr,b for the informed consent discussion.

9.2 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. At the 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 without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.
- 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.
- Risks and potential benefits of participation in the study.
- The volunteer's samples may be sent outside of Bangladesh to collaborating laboratories. These samples will be de-identified.
- The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their medical practitioner or other independent parties to decide whether they will participate in the trial.
- That future use of samples after the trial is over for other ethically approved research is optional.

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 or thumbprint. An appropriately trained and delegated clinician who was responsible for discussing consent with the participant will also sign and date the consent document. As per Bangladesh guidelines the participant will sign 2 copies of the consent form: one original copy of the signed informed consent will be given to the participant and the other original signed ICF form will be retained at the study site.

An impartial witness, independent of the study team, will attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant and that informed consent was freely given. The impartial witness will also sign and date the consent form.

9.3 Screening and Eligibility Assessment

Following informed consent, potentially eligible participants will continue to be screened until the required number of participants have been found to be eligible, randomised and vaccinated. Participants withdrawn for any reason before randomisation will be replaced, whereas participants withdrawn for any reason after randomisation will not be replaced.

Once informed consent has been given, the following information will be collected during the screening visit:

- Participant demographics (age, sex and ethnicity)
- Medical history
- Vaccination history – specifically focused on:
    - Prior receipt of adenovirus-based vaccines (i.e. Oxford AstraZeneca, Sputnik, or Janssen COVID-19 vaccines) at any time
    - Recent vaccinations (received within the preceding 3 months or planned to be received during the trial period)
- 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 (including over the counter medications, vitamins, illicit drug use and herbal supplements) and prior medications (in the preceding 12 months)
- Recording of 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 8.5)
- Blood samples for: full blood count, urea and electrolytes, liver function tests, serology for HIV, hepatitis C and hepatitis B

To be eligible for randomisation (or non-random allocation to the lead-in cohort) and vaccination, participants must meet all the inclusion criteria and none of the exclusion criteria for the study. The investigator should always use good clinical judgement in considering a participant's overall eligibility based on the inclusion and exclusion criteria.

9.3.1 Screen Failures

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.

9.4 Group Allocation and Randomisation

The first six participants will be non-randomly enrolled into the initial lead-in cohort. Following this, participants in the main trial cohort will be 5:5:2 randomised to the treatment arms listed in section 7.1.

Randomisation will only take place after a final eligibility assessment at the D0 (first vaccination) visit. Eligible participants will be randomised to the treatment arms listed in section 7.1. Randomisation will be performed using an electronic system within REDCap (or equivalent electronic database). A computer-generated randomisation list will be prepared by the study statistician. Block randomisation will be used. Randomisation will be performed at the Vac1 visit (first vaccination visit) following the final eligibility check.

9.5 Blinding and Unblinding

The sentinel lead-in cohort of 6 participants will not be blinded. All other participants within the study will be participant-observer blinded.

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 Chief Investigator). Access to the randomisation and vaccination electronic case report form (eCRF) of the study database will be user-access restricted to the unblinded vaccination team. Steps to maintain blinding of the investigational medicinal product (IMP) with the use of a placebo are detailed in section 10.4.

In the event that accidental unblinding of any blinded study team member or participant occurs, this would be recorded as a protocol deviation. The impact on the analysis or interpretation of the results will be documented as part of any subsequent analysis.

In the case of a medical emergency the study site principal investigator will have 24/7 access to unblinding of participants through an appropriate process that will be detailed in study related SOPs/documentation. This will allow emergency unblinding to occur locally, independent of the sponsor, in the case of medical emergencies. Unblinding may also be recommended by the Chief

Investigator and/or Data Safety and Monitoring Board (DSMB) following a serious adverse event (SAE), serious adverse reaction (SAR), or serious unexpected adverse reaction (SUSAR).

9.6 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.

9.6.1 Screening Visit

Participants will be required to attend a screening visit, where the screening procedures described in section 9.3 will be performed.

9.6.2 Vaccination Visits

Vaccination visits will be held at the study site. Vaccination visits require the procedures as listed under section 4.2 (Schedule of Procedures Table: Vaccination and Follow up Visits). These include:

- 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 oral temperature, pulse and blood pressure
- Perform urinary pregnancy test for females of childbearing potential (section 8.5) (prior to vaccination)
- Perform blood draw (as per section 9.7) (prior to vaccination)
- Randomisation (Main Cohort only. The initial 6 participants will be non-randomly enrolled to the lead-in cohort)
- Administer vaccine or placebo by IM injection into the deltoid muscle (ideally the non-dominant arm)
- Post-vaccination observation of volunteer at the study clinic for a minimum of 30 minutes following vaccine administration
- (On the second vaccination visit) review of AEs and SAEs since the last visit

9.6.3 Follow-Up Visits

Follow-up visits require the procedures as listed under section 4.2 (Schedule of Procedures Table: Vaccination and Follow up Visits). These include:

- Ensure that participant consent remains valid and verbally confirm continued consent
- Review of concomitant medications and other vaccinations since the last visit
- Review of AEs/AESIs/SAEs, as appropriate, since the last visit
- Review laboratory blood tests reports
- Record oral temperature, pulse and blood pressure
- Perform blood draw (as per section 9.7)

9.6.4 Daily Community visits

Community visits will occur in the evening of the day of vaccination and subsequently daily in the week following each vaccination as indicated under listed under section 4.2 (Schedule of Procedures Table: Vaccination and Follow up Visits). Trained study staff will collect and record solicited and unsolicited adverse events during these visits.

9.6.5 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 for any illness or other investigations if clinically relevant.

9.6.6 Missed Visits

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

9.7 Participant Samples

9.7.1 Clinical Laboratory Samples

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

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

9.7.2 Immunology Samples

9.7.2.1 icddr,b and University of Oxford Research Laboratories

Nipah glycoprotein G-specific serological response will be measured by ELISA and Nipah neutralising antibody responses measured by pseudovirus neutralisation assays. Additional exploratory immunogenicity assessments may include live neutralisation assays, systems serology, and cellular immune responses to Nipah virus measured by IFN-g ELISPOT, ICS, proliferation and/or whole blood assays. Human Leukocyte Antigen (HLA) typing may be performed.

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.

Immunology assays will primarily be conducted at icddr,b. Assays may additionally be run at the University of Oxford for the purposes of validation and standardisation. Additionally, some exploratory immunogenicity assessments may be conducted at the University of Oxford

9.7.2.1 Samples for non-clinical studies

Participant samples from this trial will be used in passive transfer studies involving non-human primates. The aims of this work will be to identify a surrogate threshold of protection that might be used for later phase clinical trials to facilitate the approval of Nipah virus vaccines. This work will be carried out in collaboration with the USA based National Emerging Infectious Diseases Laboratories, a facility of Boston university.

9.7.2.2 Other Research Laboratories

Collaboration with other specialist laboratories including laboratories at the trial site(s), other sites within Bangladesh, UK, USA and other countries for further exploratory immunological tests may occur. This may involve the potential transfer of serum, plasma and/or 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.

9.7.3 Urine Samples

For female participants of childbearing potential only, urine will be tested for human chorionic gonadotrophin (hCG) at screening and immediately prior to each vaccination.

9.7.4 Retention of Samples

Participants will be informed that they may opt in to the Oxford Vaccine Centre (OVC) Biobank (REC 21/SC/0161) and /or the icddr,b Bio-repository to allow long-term storage of biological samples collected under the NIV002 protocol for use in possible future research once the study closes. Participants will be informed that declining to take part in the OVC Biobank study or declining long-term storage (at icddr,b) after the end of the trial 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 outside of Bangladesh will be destroyed or returned to icddr,b after the required period of storage to meet Good Clinical Practice (GCP). If a participant elects to decline to take part in the icddr,b Bio-repository their samples will be destroyed at the end of the trial.

In accordance with country guidelines, where consent for long-term storage of samples is provided, icddr,b permits sample storage for up to 5 years following the conclusion of the trial. For storage beyond this period, additional approval must be obtained (from the appropriate ethics committee). This policy also applies to samples stored as part of the Oxford Vaccine Centre Biobank study.

9.8 Discontinuation/Withdrawal of Volunteers

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

- The investigator considers it necessary for participant safety
- Significant non-compliance with study requirements

In circumstances pertaining to the safety of the participant, the Investigator (either with or without the recommendation of the DSMB) 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 8.5)
- 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.

10 INVESTIGATIONAL PRODUCTS

All participants will receive the interventions as scheduled for their allocated group, as detailed in section 3.

10.1 ChAdOx1 NipahB

ChAdOx1 NipahB has been formulated and vialed under Good Manufacturing Practice conditions at the Serum Institute of India. The dose of ChAdOx1 NipahB to be used in trial will be 5 x 10^{10} virus particles per administration. ChAdOx1 NipahB will be administered intramuscularly. Full details of vaccine handling and administration will be detailed in an SOP. The ChAdOx1 NipahB vaccine will be manufactured, packaged, labelled and supplied by the Serum Institute of India and are labelled with a label specifying ”for clinical trial use only”. ChAdOx1 NipahB will be delivered and stored at the study site(s) pending authorised release for use in the clinical trial.

10.1.1 Storage of ChAdOx1 NipahB

ChAdOx1 NipahB will be stored in accordance with the manufacturer’s instruction. Supply of study medication to 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.

10.2 Inactivated Polio Vaccine

A WHO pre-qualified inactivated polio vaccine will be used as a control vaccine in this trial. The approved inactivated polio vaccine will be obtained from an appropriate supplier. The inactivated

polio vaccine will be administered intramuscularly. The product is a suspension of formaldehyde-inactivated and purified virus, filled into vials. The dose for a single dose administration is 0.5 ml. The vaccine is available in either single dose vials or a 2.5ml multi-dose vials.

10.2.1 Storage of Inactivated Polio Vaccine

The vaccine will be stored in temperature monitored refrigerators in accordance with the manufacturer's instructions as specified in the product SmPC which are to store at 2–8 °C and to not freeze. Multi-dose vials containing 2.5 ml vaccine (5 doses) should be stored at 2–8 °C after opening and used within 28 days.

10.3 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 the manufacturer's instructions. Saline will be administered intramuscularly.

10.4 Blinding of IMPs

ChAdOx1 NipahB, inactivated polio vaccine 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, inactivated polio vaccine 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.

10.5 Compliance with Trial Treatment

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

10.6 Accountability of The Trial Treatment

The investigator (or pharmacist) will receive the vaccine and ensure that they been transported as per the manufacturer's guidelines. The investigator or pharmacist will also maintain an inventory and acknowledge receipt of all shipments of IMP and comparator.

Storage temperatures will be monitored and recorded at site, during transport to and from the study clinics and during a clinic session, as per trial SOPs. The number of doses of study vaccines that are received, used and wasted will be documented daily during the trial and checked weekly.

Unused vaccines at the end of the trial may be retained for laboratory use only (such as laboratory assay development) or destroyed. Any recall of study vaccines required for use in the study or reporting of defective vaccines will be performed according to trial SOPs.

10.7 Concomitant Medication

All prescribed or over the counter concomitant medication, will be recorded. Concomitant medication that will result in temporary exclusion or withdrawal of participants from further vaccination are detailed in section 8.3. There is otherwise no restriction on the use of concomitant medication.

10.8 Emergency Medication and Procedures

All clinical staff will be trained and will be able to provide evidence of competency in the acute management of anaphylaxis reactions including the use of intra-muscular adrenaline. This will be detailed in relevant site SOPs and adrenaline will be 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 from the time of vaccination for cohort 1 and for cohort 2 from the time of randomisation to the participants last visit. These will include the list below (Table 4). Additionally, other adverse events (i.e. not listed below) may also be categorised by investigators as AESIs if scientifically warranted.

Table 4 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 vaccines or study procedures must be determined by a PI-delegated blinded clinician / Investigator. The relationship of the adverse event with the study products will be categorized as not related, possibly related, probably related or definitely related.

The delegated clinician will use clinical judgement to determine the relationship using the following definitions (Table 5):

Table 5 Guidelines for assessing the relationship of vaccine administration to an Adverse Event (adapted from the World Health Organization – Uppsala Monitoring Centre Causality Assessment System[36])

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 the severity grading scales are listed in Appendix B: Severity Grading Scales.

11.6 Procedures for Collecting and Recording Adverse Events

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 each vaccination for 28 days.

11.7 Solicited Adverse Events

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

Table 6 Solicited Adverse Events

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

11.8 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.

11.9 Observation (Vital Signs) AEs

Physical observations of the patient (e.g. temperature, blood pressure, heart rate) will be taken according to the schedule of procedures. If abnormal and assessed as clinically significant, a severity grading will be assigned as per Appendix B: Severity Grading Scales.

11.10 Laboratory AEs

Severity gradings 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.

11.11 Notes on Recording AEs

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

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

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect 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 DSMB with the ongoing consent of the participant.

11.12 Following Up of AEs

AEs considered related to the vaccines or placebo and any AE that results in a participant's withdrawal from the study 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.

11.13 Reporting Procedures for SAEs

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

All SAEs will be reported to the Chief Investigator (as delegated by the Sponsor), ERC and DGDA immediately (or within 24 hours of site awareness 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 Chief Investigator on behalf of the Sponsor will be responsible for unblinding in the event of serious adverse reactions, except where there is a medical emergency where site PI can unblind without sponsor permission (as detailed in section 9.5).

Unrelated SAEs will be reported to both the local and international DSMBs for discussion at the next scheduled DSMB review (11.20.2).

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

The DSMB will perform an independent review of SAEs and request any further information required in a manner adherent to the procedures and timelines of the DSMB Charter. Documentation of this review will be kept in the TMF.

11.14 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.

11.15 SUSAR Reporting

All SUSARs will be reported to the sponsor (University of Oxford) delegate; the local and international DSMB, icddr,b IRB, Bangladesh DGDA, relevant Ethics Committee and other applicable health authorities based on applicable legislation. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days. Treatments will be unblinded for participants experiencing SUSARs.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

11.16 Development Safety Update Report

The sponsor delegate will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority, Ethics Committee, Host Organisation and Sponsor.

For assessment of SARs in the DSUR, the RSI that was approved at the start of the safety reporting period will be used. When there have been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ from the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting. 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).

11.17 Safety Profile Review

The safety profile will undergo blind review on a regular basis by the Investigators/Sponsor team assessing adverse events and safety blood data. Any concerns will be referred to the blinded Principal and Chief Investigator. If the Principal or Chief Investigator remains concerned, they may consider unblinding and/or escalation to the unblinded DSMB as required.

11.18 Trial Management Group

The Chief Investigator, study investigators, senior staff at the co-ordinating centre, and Sponsor delegates will form the trial management group (TMG) and will provide on-going management of the trial.

11.19 Data Safety Monitoring Board (DSMB)

An international data safety monitoring board (iDSMB) will be established to assess at intervals the progress of the trial and the safety of the study agent across the ChAdOx1 NipahB development program. The iDSMB will include representatives from Bangladesh, including a member of the local icddr,b Ethical Review Committee (ERC), and a member of the local DSMB (below). Appointed by the Sponsor, the iDSMB will comprise independent members and will operate in accordance with a trial specific iDSMB charter. The iDSMB will formally review both safety and immunogenicity data. A non-voting observer member from Safety Platform for Emergency vaccines (SPEAC) - a vaccine safety organisation that is a collaboration between the Brighton Collaboration and CEPI - will also attend the iDSMB.

The study will also be monitored by a DSMB constituted by icddr,b with input from the icddr,b Ethical Review Committee (ERC). The local DSMB will include representation outside of icddr,b. The local DSMB is expected to convene once prior to the start of the study after ethical and regulatory approval of the study protocol and will additionally convene for the meetings as detailed in section 11.20.2 (DSMB Reviews). The local DSMB will operate in line with the icddr,b ERC DSMB guidelines. Some of the DSMB members from Bangladesh will contribute to both the local and international DSMB committees. The local DSMB will provide ongoing review of safety data during the delivery of NIV002, in conjunction with the international DSMB. The local DSMB will not undertake formal reviews of immunogenicity data.

In addition, a physician in Bangladesh with relevant study-related or therapeutic expertise will be identified as an Independent Safety Monitor (ISM). The ISM will not be an investigator for this study. Circumstances may arise where an independent medical assessment of a participant may be warranted. In such circumstances, the identified ISM would be requested to carry out an independent assessment of the participant.

11.20 Interim Safety Reviews

11.20.1 Sequence of Enrolment and Vaccination

The lead-in cohort of 6 participants will be enrolled and receive their first vaccine prior to the enrolment of further volunteers. Enrolment of the NIV002 main cohort participants will only begin after a positive decision from the local DSMB following the first DSMB safety review as detailed below (section 11.20.2).

11.20.2 DSMB Reviews

DSMB data reviews will be done as follows:

1. (local DSMB only) Formal review of the safety profile after 7 days of safety data has been collected from the first 6 participants (the lead-in cohort) after they have received the first dose of vaccine. This review (by the local DSMB) will decide on progression to administering the first vaccine to the remaining participants in the trial.
2. (local DSMB and international DSMB) Formal review of the 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 DSMB review. The international DSMB will also review the immunogenicity data at this point.

3. (local DSMB and international DSMB) Formal review of the safety profile including data up to 28 days after the second dose of vaccine has been administered to all participants. The trial will continue in parallel to this DSMB review. The international DSMB will also review the immunogenicity data at this point.
4. (local DSMB and international DSMB) Independent review following any SAE deemed to be related to the trial active vaccine or placebo.
5. (local DSMB and international DSMB) Unscheduled reviews on request of the study management committee at a frequency determined by the severity of reported adverse events.

From these reviews the local and international DSMBs will make recommendations to the study investigators on whether there are any ethical or safety reasons why the trial should not continue (except for review 1, which will be undertaken by the local DSMB only). A summary of all blinded and unblinded AEs and SAEs to date will be provided (to either local or international) DSMBs on request.

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

11.21 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.

11.22 Safety Holding Rules

11.22.1 Group Holding Rules

11.22.1.1 Group Holding Rules (Lead-in cohort)

The lead-in cohort 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.

11.22.1.2 Group Holding Rules (Main cohort)

The group holding rules for the main cohort are as follows:

- **Solicited local adverse events**:
    - If 10% 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 10% 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 10% 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.

11.22.1.3 Group Holding Rules Additional Details

If a holding rule has been met, the Chief Investigator on behalf of the Sponsor will inform the regulatory authority. The DSMB will be asked to review relevant safety data and provide a recommendation on further dosing. If the DSMB recommend to restart dosing, the request (with pertinent data) must be approved by the regulatory authority prior to restarting dosing. The DSMB 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.

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 either the local or international DSMB, Chief Investigator, 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.

11.22.2 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 or they may be discontinued from further vaccination in 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; details will be fully described in the Data Management Plan, in compliance with GCP requirements and relevant SOPs.

The Investigators will populate the content of the participants' CRFs, which will be in an electronic format (eCRF) using a REDCap database. Backup paper versions of the REDCap CRFs will also be available but will only be used in the event of technical issues or system downtime. This database will

be stored on a secure icddr,b server and will have restricted user specific access and accountability records. Critical data will be backed up on secure University of Oxford servers. All information transcribed to and from the database will be done by encrypted (Https) transfer. Access to the study's database will be restricted to the members of the study team by username and password.

Each study participant will have a unique participant number which will be allocated at the time a screening visit is booked. Names and/or identifying details are not included in any study data electronic file. After enrolment the participants will be identified by a study specific participant number and/or code.

12.1 Data Integrity

Data collection and storage will be inspected throughout the study by monitoring arranged by sponsor or authorised representatives of the sponsor. Trial data may also be audited.

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) or as outlined in local SOP'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, subject to clinical trial regulations. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review. Pseudo-anonymised research data may be stored indefinitely not due to regulatory requirements but for the scientific benefit.

12.3 Source Data

Source documents are original documents, data, and records from which participants' eCRF data are populated. These may include, but are not limited to, hospital or medical records (from which medical history and previous and concurrent medication may be summarised into the eCRF), clinical and office charts, laboratory and pharmacy records, radiographs, physician prescriptions 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 in a locked cabinet.

The site 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 participants provide specific consent, we will use personal identifiable data to invite participants for future related research.

13 STATISTICS

13.1 Statistical Analysis Plan

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP) that will be available and finalised before any formal analysis of the data takes place.

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.

Descriptive statistics relating to participant characteristics at baseline will be calculated overall and by randomised groups. No formal statistical comparisons of baseline characteristics between randomised groups will be conducted.

Counts and percentages of participants with local and systemic solicited adverse reactions from the trial database 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.

The humoral antibody data is expected to be log normal distributed and 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. Seroconversion rate, defined as the percentage of participants with 4-fold rise before and after vaccination(s), along with corresponding 95% CIs. Participants with baseline antibody level (before vaccination) of below the lower limit of detection (LLOD) and become above the LLOD following vaccination (s) will also be considered as seroconversion.

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

13.1.2 The Number of Participants

306 participants will be enrolled into the study. Participants are only considered enrolled once they were randomised. Recruitment will continue until 306 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. With 250 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 1%.

13.2 Study populations

The analysis populations are defined:

Populations	Description
Screening Set	The screening set consists of all participants screened.
Safety analysis set	Participants who have received the first dose (regardless of screening, randomisation or allocation) For solicited AE analysis, participants with missing data on all symptom diaries following a dose will be excluded from the analysis of that dose.
Full Analysis Set (FAS)	The FAS consists of all randomised participants who received the study IMP or comparator. Participants will be analysed according to their randomised arms.
Per-protocol set	The per-protocol set consists of all participants in the FAS whose endpoints are available. Participants will be analysed according to their IMP or comparator received. Per-protocol set will be considered as the primary analysis population for primary and secondary immunogenicity outcomes.

13.3 The Level of Statistical Significance

There will be no testing for any hypotheses, analyses will be purely descriptive and hypothesis generating. All confidence intervals for descriptive analyses will be set at 95%.

13.4 Criteria For Termination of the Trial

The sponsor or Chief Investigator, with or without the DSMB's recommendation, 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, regulatory authorities and relevant Ethics Committees will be notified within 15 days of this occurring.

In the event of the trial being terminated early, follow-up of enrolled participants may 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.

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

All available data will be used in the analysis. There will no data imputation for the primary and secondary outcomes.

13.6 Procedures for Reporting Any Deviation(s) from the Original Statistical Plan

A final statistical analysis plan (SAP) will be signed off before the final database lock. Any additional analysis or deviations from the SAP will be documented in the final analysis report and updated according to the statistical standard operating procedure.

13.6.1 Inclusion in Analysis

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

13.6.2 Interim Analysis Timing

We are planning to conduct two analyses for this study. The first analysis (interim analysis) will be carried out when the primary immunogenicity data become available (cleaned and locked) following completion of the Vac2+28 visits by all participants that remain in the trial. The first analysis will cover the two primary endpoints, safety endpoints (including solicited AEs, unsolicited AEs in 28 days following vaccination, and all the other safety data before the data lock following completion of the Vac2+28 visits), and all the available immunogenicity data (full dataset for the whole study population, partially available immunogenicity data will not be included). The final analysis will be conducted on the completion of the study and will further include additional safety data till the end of the study follow-up and all the other available exploratory endpoints. There is no stopping rule for the interim analysis and the analysis will not affect the continuation of the study.

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

The protocol, informed consent form, and participant information sheet will be submitted to Oxford Tropical Research Ethics Committee (OxTREC), icddr,b Research Review Committee (RRC) and icddr,b Ethical Review Committee (ERC) for review and written approval. The protocol will also be approved by the Directorate General of Drug Administration (DGDA).

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 Chief Investigator 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 Chief Investigator or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

14.5 Reporting

The Chief Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation, ERC, DGDA funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the same parties.

14.6 Participant Confidentiality

The investigators, sponsor and all staff from organisations involved with the implementation of the trial must ensure that the participant's confidentiality is maintained. Personal identifiers will not be included in any study report. All study records will be kept confidential to the extent provided by national and local laws. Medical records containing identifying information may be made available for review when the study is monitored by CRO or an authorized regulatory agency. Direct access may include examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

When appropriate and to the extent possible, study procedures will be conducted to protect participant privacy and confidentiality.

All study-related information will be stored securely at the study site. All participant identifiable information will be stored in locked file cabinets in areas with access limited to study staff and authorised personnel. Data collection, administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. All databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link Participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access. Participant's study information will not be released without their written permission, except as necessary for monitoring or audit. Approval to provide such information to external bodies for the purposes of monitoring and audit will be sought as part of the informed consent process.

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so and Bangladesh data protection laws. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). The study staff will safeguard the privacy of participants' personal data.

14.7 Participant Financial Compensation

Participant will be reimbursed for travel to study visits or transport will be provided for study visits in line with local approved procedures. Participant's wage loss will be provided for scheduled study visits (approximately $8.00 per visit). The study ICF will state the plan for reimbursement. Participants will

not be charged for study vaccinations, research clinic visits, research-related examinations, or research-related laboratory tests. While enrolled in the study, medical care will be provided by the study team in line with local good medical practice and participants will not need to pay for this. At the end of the study, participants will be referred to an appropriate health care provider for any ongoing treatment needed which is judged to be unrelated to trial participation. The trial team will not pay for long term treatment of unrelated conditions diagnosed during the trial. For participants who are found to be ineligible for any reason during screening, immediate care will be provided for any health conditions in line with good local medical practice. The participant will then be referred on to an appropriate local health care provider for ongoing care. The trial team will not pay for ongoing treatment in this case.

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. 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/authorised/delegated representatives of 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. Major protocol deviations will be reported to the Bangladeshi ERC as they occur. All others will be reported as line listing in the annual progress report.

15.5 Audit and Inspection

The Oxford Vaccine Group Quality Assurance team operates an internal audit program to ensure that the systems used to conduct clinical research are present, functional, and enable research to be conducted in accordance with study protocols and regulatory requirements. Audits include laboratory activities covering sample receipt, processing and storage and assay validation. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor.

The Sponsor, trial site(s), CEPI, 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 local Regulator or Sponsor to ensure compliance with protocol as amended. The Sponsor will assist in any inspections and will support the response to the Regulator 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

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

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

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the Chief Investigator the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and any relevant host organisation within seven calendar days.

18 PUBLICATION POLICY

The investigators will co-ordinate dissemination of data from this study. All publications, including manuscripts, abstracts, oral/slide presentations, and book chapters, etc., based on data from this study will be reviewed by each sub-investigator prior to submission. Authors will acknowledge that the study was funded by CEPI. The investigators will co-ordinate dissemination of data from this study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. 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	Confidence Interval
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
DSMB	Data Safety Monitoring Board
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
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
IB	Investigators Brochure

Abbreviations	
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
SmPC	Summary of Product Characteristics
SOC	System Organ Classes

Abbreviations	
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

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22 Appendix A: Investigator Signature and Declarations

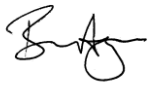
Statement of Compliance

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

Chief Investigator Approval, Agreement and Conflict of Interest statement

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

Conflict of interest statement: I declare that there is no potential of interest

Chief Investigator	**Signature**	**Date:**
Prof Brian Angus		**20/08/2025**

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: I declare that there is no potential of interest

Lead Statistician	**Signature**	**Date:**
Prof Xinxue Liu		**20/08/2025**

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: I declare that there is no potential of interest

Principal Investigator	Signature	Date:
K Zaman	Kzaman	04 SEP 2025

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23 Appendix B: Severity Grading Scales

Table 7 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
Swelling at injection site	1	2.5 – 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis

Table 8 Severity grading criteria for local and systemic AEs.

GRADE 0	None
GRADE 1	Mild: Transient or mild discomfort: 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 9 Severity grading criteria for physical observations (applies to adults only). *Taken after ≥10 minutes at rest **When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterising bradycardia among some healthy subject populations, for example, conditioned athletes. ***Only if symptomatic (e.g. dizzy/ light-headed)

Vital Signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially Life threatening
Fever (oral)	38.0°C - 38.4°C	38.5°C – 38.9°C	39.0°C - 40°C	> 40°C
Tachycardia (bpm)*	101 - 115	116 – 130	>130	A&E visit or hospitalisation for arrhythmia
Bradycardia (bpm)**	50 – 54	45 – 49	<45	A&E visit or hospitalisation for arrhythmia
Systolic hypertension (mmHg)	141 - 150	151 – 155	≥155	A&E visit or hospitalisation for malignant hypertension
Diastolic hypertension (mmHg)	91 - 95	96 – 100	>100	A&E visit or hospitalisation for malignant hypertension
Systolic hypotension (mmHg)***	85 - 89	80 – 84	<80	A&E visit or hospitalisation for hypotensive shock
Respiratory Rate (breaths per minute)	17 - 20	21-25	>25	Intubation

Table 10 Grading Scale for Laboratory AEs, based on The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events. Version 2.1 July 2017

	Laboratory reference range (icddr,b)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life threatening)
Haemoglobin (female): decrease from baseline value (g/dl)	12.0 – 15.0	1.0 – 1.5	1.6 – 2.0	2.1 – 5.0	≥5.1
Haemoglobin (male): decrease from baseline value (g/dl)	12.0 – 15.0	1.0 – 1.5	1.6 – 2.0	2.1 – 5.0	≥5.1
Haemoglobin (female): absolute value (g/dl)	12.0 – 15.0	9.5 – 10.4	8.5 – 9.5	6.5 – 8.4	≤6.4
Haemoglobin (male): absolute value (g/dl)	12.0 – 15.0	10.0 – 10.9	9.0 – 10.0	7.0 – 8.9	≤6.9
White Blood Cells elevated ($x10^9$/L)	4.00 – 11.00	11.50 – 15.00	15.01 – 20.00	20.01 – 25.00	≥25.01
White Blood Cells decreased (x10^9)	4.00 – 11.00	2.00 – 2.50	1.50 – 1.99	1.00 – 1.49	≤0.99
Lymphocytes decreased ($x10^9$/L)	1.5 – 4.0	0.7 – 0.99	0.5 – 0.69	0.25 – 0.49	≤0.24
Eosinophils ($x10^9$/L)	0.04 – 0.45	0.6 – 1.50	1.51 – 5.00	≥5.01	Hypereosinophilia
Neutrophils, decreased ($x10^9$/L)	2.0 – 7.5	0.8 – 1.00	0.60 – 0.79	0.40 – 0.59	≤0.39
Platelets, decreased ($x10^9$/L)	165 – 415 (F), 150 – 450 (M)	100 – 125	50 – 99	25 – 49	≤24
Sodium: hyponatraemia (mmol/L)	136 – 145	130–134	125 – 129	121 – 124	≤120
Sodium: hypernatraemia (mmol/L)	136 – 145	146 – 149	150 – 153	154 – 159	≥160
Potassium: hyperkalaemia (mmol/L)	3.5 – 5.1 (serum), 3.5 – 4.5 (plasma)	5.6 – 6.0	6.0 – 6.4	6.5–6.9	≥7.0
Potassium: hypokalaemia (mmol/L)	3.5 – 5.1 (serum), 3.5 – 4.5 (plasma)	3.0 – 3.3	2.5 – 2.9	2.0 – 2.4	≤1.9
Urea (mmol/L)	2.8 – 7.2	8.4–8.9	9.0 –11	>11	Renal replacement therapy
Creatinine (µmol/L) (Male)	64 – 104	114 – 135	136 – 187	188 – 364	≥365
Creatinine (µmol/L) (Female)	49 – 90	99 – 117	117 – 162	162 – 315	≥315
ALT (IU/L) (male)	<50	63 – 125	126 – 250	251 – 500	≥501
ALT (IU/L) (female)	<35	44 – 88	89 – 175	176 – 350	≥351
Bilirubin, total (µmol/L)	5 – 21	23 – 34	35 – 55	56 – 105	≥106
Alkaline phosphatase (IU/L)	30 – 120	150 – 300	301 – 600	601 – 1200	≥1201
Albumin: hypoalbuminaemia (g/L)	35 – 52	30 – 34	20 – 29	≤19	Not applicable

24 Appendix C: Severity grading of respiratory, cardiovascular and gastrointestinal diseases

Cardiovascular Diseases

New York Heart Association (NYHA) functional classification (Ref: Davidson's Principles and Practice of Medicine, 24th Edition-2022)	
Class **I (Mild)**	No limitation of physical activity. Ordinary activity doesn't cause undue fatigue, palpitations, or shortness of breath.
Class **II (Mild-to-Moderate)**	Slight limitation of physical activity. Comfortable at rest, but ordinary activity causes fatigue, palpitations, or shortness of breath.
Class **III (Moderate-to-Severe)**	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitations, or shortness of breath.
Class **IV (Severe)**	Unable to carry on any physical activity without discomfort. Symptoms present even at rest, and any activity worsens them.

Respiratory Diseases

Modified Medical Research Council (MRC) dyspnoea scale (Ref: Davidson's Principles and Practice of Medicine, 24th Edition)	
Grade	**Degree of breathlessness related to activities**
0	No breathlessness except with strenuous exercise
1	Breathlessness when hurrying on the level or walking up a slight hill
2	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own pace
3	Stops for breath after walking ~100 m or after a few mins on level ground
4	Too breathless to leave the house, or breathless when dressing or undressing

Gastrointestinal Diseases

Child-Pugh classification of prognosis in cirrhosis (Ref: Davidson's Principles and Practice of Medicine, 24th Edition-2022)			
Score	1	2	3
Encephalopathy	None	Mild	Marked
Bilirubin (µmol/L(mg/dL))*			
Primary biliary cholangitis/sclerosing cholangitis	< 68 (4)	68–170 (4–10)	> 170 (10)
Other causes of cirrhosis	< 34 (2)	34–50 (2–3)	> 50 (3)
Albumin (g/L (g/dL))	> 35 (3.5)	28–35 (2.8–3.5)	< 28 (2.8)
Prothrombin time (secs prolonged)	< 4	4–6	> 6
Ascites	None	Mild	Marked
Add the individual scores: < 7 = Child's A, 7–9 = Child's B, > 9 = Child's C			
*To convert bilirubin in µmol/L to mg/dL, divide by 17.			

Renal Diseases

Stages of chronic kidney disease (CKD) (Ref: Davidson's Principles and Practice of Medicine, 24th Edition-2022)		
Stage[1]	**Definition**[2]	**Description**
1	Kidney damage[3] with normal or high GFR (> 90)	Normal function
2	Kidney damage and GFR 60–89	Mild CKD
3A 3B	GFR 45–59 GFR 30–44	Mild to moderate CKD Moderate to severe CKD
4	GFR 15–29	Severe CKD
5	GFR < 15 or on dialysis	Kidney failure
[1] Stages of CKD 1–5 were originally defined by the US National Kidney Foundation Kidney Disease Quality Outcomes Initiative 2002. In the 2013 Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD guideline update, the suffices A1, A2 and A3 are recommended, indicating the presence of albuminuria of < 30, 30–300 and > 300 mg/ 24 hrs respectively, in view of the prognostic importance of albuminuria. [2] Two GFR values 3 months apart are required to assign a stage. All GFR values are in mL/ min/1.73 m^2. [3] Kidney damage means pathological abnormalities or markers of damage, including abnormalities in urine tests or imaging studies.		

Appendix D: Document History

Version	Date		Author	Changes
1.0	20 DEC 2024		Daniel Jenkin, Sarah Kelly, Brian Angus, Ilsa Haeusler, Rachel Kenneil, Dr K Zaman	Document created
1.0	11 FEB 2025		Daniel Jenkin, Sarah Kelly	Minor text updates and clarifications: • Full title updated ("years" added) • Short title updated ("years" added) • List of investigators updated • Impact of Nipah and the Need for a Vaccine section – updated case numbers and additional reference added

				• Trial Design section – correction of 2A and 2B allocation and text clarification • Pregnancy and Contraception section – “Trial team will arrange for acceptable forms of contraception…” sentence replaced • Clinical Laboratory Samples section – insertion of reference to “icddr,b Diagnostic laboratory” • Reporting procedures for SAEs section – text clarifications • Data Safety Monitoring Board (DSMB) section – text clarifications • Approvals section – text clarifications
1.0	12 MAR 2025		Daniel Jenkin	Changes following icddr,b Research Review Committee review: • Addition of rationale for inclusion of cohort 1
1.1	05 MAY 2025		Lilli Hahn	Changes following icddr,b Ethical Review Committee: • Addition of Appendix C (Severity grading of respiratory, cardiovascular, renal, and gastrointestinal diseases) • Updated numbering of this table from Appendix C to Appendix D, as well as updating of the ToC