7.4.6. Symptomatic participants

Participants who become symptomatic during follow-up will be instructed to call the study team who will then advise on how to proceed with clinical testing for SARS-COV-2 infection if necessary, as per the trial working instructions. Participants will get weekly reminders (text messages) to get in touch with the study team if they manifesting any of the symptoms indicated in Table 4; or if they are admitted to hospital for any reason. At the COVID-19 testing visit, a nasal swab and/or saliva, blood samples for safety (FBC, Biochemistry, CRP, others if deemed clinically relevant) and immunology, vital signs and other clinical data will be taken. Symptomatic participants may be regularly reviewed over the phone, or in-person if required. Participants will be asked to attend a follow-up visit or have a telephonic call 5 days (±2 days) post SARS-CoV-2 testing for clinical review and further testing if applicable (i.e. worsening or non-resolution of clinical symptoms) if the initial test result was negative for SARS-CoV-2. For participants that initially tested negative and who test positive for SARS-CoV-2 on a repeat swab, the participant will be followed-up as detailed below.

For participants that are confirmed to be infected with SARS-COV-2, repeat nasal swab or saliva sampling (preferably self-administered) and blood samples (for immunology assays) will be obtained at Days 5-8, 12-15 and 28-35 days.

All participants investigated for SARS-CoV-2 on an ambulatory basis, will be required to complete a diary card reporting on daily signs and symptoms for at least seven days from day on which sampled, and recording of the resolution date of the signs and symptoms if the illness duration exceeds 7 days. For hospitalized participants, clinical information will be sourced from the participant or medical records, through to hospital discharge and/or resolution of the illness. Any documented molecular test result confirming SARS-CoV-2 infection of study participants done as part of standard of care will be used as confirmatory evidence of confirmed COVID-19 illness.

7.4.7. Medical notes review

With the participant's consent, the study team will request access to medical notes or submit a data collection form for completion by attending clinical staff on any medically attended COVID-19 episodes. Any data which are relevant to ascertainment of efficacy endpoints and disease enhancement (AESI) will be collected. These are likely to include,

but not limited to, information on ICU admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, imaging and blood tests results, amongst others.

7.4.8. Randomisation, blinding and code-breaking

Participants will be randomised to investigational vaccine or placebo (0.9% NaCl) in a 1:1 allocation, using block randomisation. Block sizes of 8 will be used for all groups (4 IP and 4 placebo).

All participants and clinical study staff, except unblinded pharmacist and vaccine dispenser will be blinded to the trial arm that participants have been allocated to, whether investigational vaccine or placebo. The trial staff administering the vaccine will not be blinded. Vaccines will be prepared out of sight of the participant and syringes will be covered with an opaque object/material until ready for administration to ensure blinding.

If the clinical condition of a participant necessitates breaking the code, this will be undertaken according to a trial specific working instruction and group allocation sent to the attending physician, if unblinding is thought to be relevant and likely to change clinical management.

8. INVESTIGATIONAL PRODUCT

8.1. Manufacturing and presentation

8.1.1. Description of ChAdOx1 nCoV-19

ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2 of 5-7.5x10^{10} vp dose.

8.2. Supply

ChAdOx1 nCoV-19 utilised in the COV001 trial was formulated and vialed at the Clinical Biomanufacturing Facility (CBF), University of Oxford. The vaccine manufacturing, packaging and labelling have been relocated to the following GMP

manufacturing facilities:

Name of Facility	Responsibility
Cobra Biologics Limited Stephenson Building Newcastle, ST5 5SP, United Kingdom	Manufacture of Drug Substance
Symbiosis Pharmaceutical Services Limited Unit 10 Scion House Stirling University Innovation Park Stirling, Scotland FK9 4NF United Kingdom	Drug Substance Lot Release Testing
Advent Societa' A Responsabilita Limitata, via Pontina KM 30,600, Pomezia (RM), 00040, Italy	Manufacture of Drug Substance Drug Substance Lot Release Testing and Stability Testing
Thermofisher Scientific, Fisher BioServices division, Unit 1, Woodside, Dunmow road, Birchanger, Bishop's Soortford, CM23 5RG, United Kingdom	Packaging, Labelling and Distribution

ChAdOx1 nCoV-19 (AZD1222) has been formulated at Cobra Biologics Ltd, vialed at Symbiosis Pharmaceutical Services, and labelled and packaged at Thermo Fisher Scientific (Hertfordshire, United Kingdom). It will be certified by a Qualified Person (QP) at the MedImmune Pharma, BV (Nijmegen, The Netherlands) or MedImmune Ltd (Cambridge, United Kingdom) before release and transfer to the clinical site. Investigational product will be managed and distributed to South African sites by a qualified IP logistics company in South Africa.

8.3. Storage

The vaccines will be stored in a restricted access refrigerator and / or freezer according to the vial batch storage conditions requirement at the clinical site. The vaccine manufactured by Advent is stored at nominal -80oC (+/- 20 oC) in a secure freezer, at the clinical site. The vaccine manufactured by Cobra Biologics Ltd is stored at 2-8°C in a

secure fridge, at the clinical site.

Vaccine Batch	Storage Conditions
Batch K.0008 Batch K.0011	-80˚C
Batch 20482B	2- 8 ˚C

All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms.

8.4. Administration

On vaccination day, ChAdOx1 nCoV-19 will be allowed to thaw to room temperature and will be administered in accordance with trial specific instructions or stored at 2-8˚C for a maximum of 6 hours, where multiple doses are required from a single vial. The vaccine manufactured by Cobra Biologics is a multi-dose vial which is stored at 2-8 ˚C and does not require thawing. If the vaccine is stored outside of 2-8˚C it must be used within 6 hours. The vaccine will be administered intramuscularly into the deltoid of the non-dominant arm (preferably). All volunteers will be observed in the unit for a minimum of 15 minutes (+15 minutes) after vaccination. During administration of the investigational products, Advanced Life Support drugs and resuscitation equipment will be immediately available for the management of anaphylaxis. Vaccination will be performed and the IMPs handled according to the relevant SOPs.

8.5. Rationale for selected dose

The dose to be administered in this trial have been selected on the basis of clinical experience with the ChAdOx1 adenovirus vector expressing different inserts and other similar adenovirus vectored vaccines (e.g. ChAd63).

A first-in-man dose escalation study using the ChAdOx1 vector encoding an influenza antigen (FLU004), safely administered ChAdOx1 NP+M1 at doses ranging from 5 x 10^8 to

5 x 10^{10} vp. Subsequent review of the data identified an optimal dose of 2.5 x 10^{10} vp balancing immunogenicity and reactogenicity. This dose has subsequently been given to hundreds of participants in numerous larger phase 1 studies at the Jenner Institute. ChAdOx1 vectored vaccines have thus far demonstrated to be very well tolerated. The vast majority of AEs have been mild-moderate and there have been no SARs until this date.

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

MERS001 was the first clinical trial of a ChAdOx1 vectored expressing the full-length Spike protein from a separate, but related betacoronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5x10^{9} vp to 5x10^{10} vp. Despite higher reactogeniticy observed at the 5x10^{10} vp, this dose was safe, with self-limiting AEs and no SARs recorded. The 5x10^{10} vp was the most immunogenic, in terms of inducing neutralising antibodies against MERS-CoV using a live virus assay (Folegatti et al. Lancet Infect Dis,2020, in press). Given the immunology findings and safety profile observed with a ChAdOx1 vectored vaccine against MERS-CoV, the 5x10^{10} vp dose was chosen for ChAdOx1 nCoV-19.

The trial conducted in the UK is the first in human assessment of the SARS-CoV 2 S antigenic insert.[16] As other batches of ChAdOx1 nCoV-19 become available, including for this ChAdOx1 nCoV-19_ZA_PhI/II trial, a staggered approach will be used for use of the first 5 vaccines of each new batch. Safety of ChAdOx1 nCoV-19 will be monitored in real time and should unacceptable adverse events or safety concerns arise, doses will be decreased via an amendment. As of 19th August 2020, a total of 9981 participants have been enrolled in the COV001/COV002 studies in the UK and 3688 in Cov003 in Brazil.

Several different batches of vaccine have been produced for the clinical trials: at Oxford University in the UK, Advent in Italy and at COBRA in the UK. Dosing of the vaccine has been based on Abs260 (Oxford and COBRA) or qPCR (Advent) depending on the manufacturers release specifications. Emerging data from 6 different assays, provides more information on the dosing and provides insight into consistency across different batches. For batch K.0008, used in South Africa, dosing was based on the qPCR data from Advent to obtain approximately 5 x 10^{10} vp as the preferred dose level. For batch K.0011 from Advent, the dose has been adjusted to an equivalent of 7.5 x 10^{10} vp on the

Advent qPCR to ensure consistency across batches with the extended panel of assays. In future Astra Zeneca will be developing the vaccine and responsible for subsequent batches, and their assays are included in the table below.

An analytical comparability assessment of ChAdOx1 nCoV-19 (AZD1222) manufactured by CBF, Advent and Cobra Biologics was conducted using a comprehensive set of physiochemical and biological release and characterization tests. In order to support the analytical comparability assessment, A260 testing of Advent's process (K.0007, K.0008, K.0009 and K.0011 lots) was performed, where corrections to the absorbance due to excess polysorbate 80 were made to compensate for polysorbate 80 concentrations above the formulation target of 0.1% (w/v). Differences in strength related attributes (ie, virus particle concentration, virus genome concentration, and infectious virus concentration) are noted. These differences in strength is further examined for potential impact on clinical dosing. The target clinical dosage of CBF's product is 5×10^{10} viral particles per dose based on vp/mL concentration determined by UV spectroscopy (A260), whereas that of Advent's product is 5×10^{10} viral genome copies per dose based on vg/mL concentration determined by qPCR. The target clinical dosage of Symbiosis' product is $3.5 – 6.5 \times 10^{10}$ viral particles per dose based on the vp/mL concentration determined by A260, with a 0.5 mL dosing volume. This dosing range is based on a target 5×10^{10} viral particles per dose and a ± 30% range to take into account process and method variabilities. The planned clinical dosage of Symbiosis' product is compared to that of CBF and Advent products, the resulting Symbiosis' product dosage at 0.5 mL for lot 20481A is somewhat lower in total viral particle per dose (20% from the lower range limit), slightly higher in total viral genome copies per dose (12% from the higher range limit), and slightly lower in total infectious particle per dose (8% from the lower range limit). These differences are considered to be comparable to or within the variabilities from the analytical methods used in concentration determination (A260, qPCR, and infectivity) and the dosing volumes during clinical administration. In summary, with a 0.5 mL dosing volume for Symbiosis' product, strength difference from CBF and Advent products is not expected to have significant clinical impact in terms of reactogenicity and immunogenicity/efficacy.

Table Clinical Strengths of AZD1222 Drug Product

Strength Attribute	Process 1		Process 2				Process 3
	02P20-01	02P20-02	K.0007	K.0008	K.0009	K.0011	20481A
Concentration							
Virus particle concentration (A_{260}) (vp/mL)	1.49×10^{11}	1.22×10^{11}	3.12×10^{11}	3.16×10^{11}	2.45×10^{11}	1.4×10^{11}	0.8×10^{11}
Virus genome concentration (qPCR) (vg/mL)	1.7×10^{11}	Not tested	1.7×10^{11}	2.1×10^{11}	1.4×10^{11}	1.5×10^{11}	1.3×10^{11}
AZ qPCR (vg/mL)	1.37×10^{11}	Not tested	1.38×10^{11}	1.42×10^{11}	1.12×10^{11}	0.67×10^{11}	0.77×10^{11}
AZ ddPCR (vg/mL)	1.17×10^{11}	Not tested	1.29×10^{11}	1.27×10^{11}	1.01×10^{11}	0.59×10^{11}	0.71×10^{11}
Infectious particle concentration (ifu/mL) [a]	2.6×10^{9}	Not tested	2.9×10^{9}	3.0×10^{9}	2.4×10^{9}	1.3×10^{9}	1.3×10^{9}
AZ Infectivity (ifu/mL)	2.13×10^{9}	Not tested	1.89×10^{9}	2.04×10^{9}	2.06×10^{9}	1.09×10^{9}	1.28×10^{9}
Target Clinical Dosage							
Equivalent DP volume per dose (mL)	0.34	0.41	0.294	0.235	0.356	0.5	0.50
Dosing of virus particle (vp/dose)	5.1×10^{10}	5.0×10^{10}	9.2×10^{10}	7.4×10^{10}	8.7×10^{10}	7×10^{10}	4.0×10^{10}
Dosing of viral genome (vg/dose)	5.8×10^{10}	NA	5.0×10^{10}	4.9×10^{10}	5.0×10^{10}	7.5×10^{10}	6.5×10^{10}
AZ qPCR (vg/dose)	4.7×10^{10}	NA	4.1×10^{10}	3.3×10^{10}	4.0×10^{10}	3.35×10^{10}	3.9×10^{10}
AZ ddPCR (vg/dose)	4.0×10^{10}	NA	3.8×10^{10}	3.0×10^{10}	3.6×10^{10}	2.95×10^{10}	3.5×10^{10}
Dosing of infectious particle (ifu/dose)	8.8×10^{8}	NA	8.5×10^{8}	7.1×10^{8}	8.5×10^{8}	6.5×10^{8}	6.5×10^{8}
AZ Infectivity (ifu/dose)	7.2×10^{8}	NA	5.6×10^{8}	4.8×10^{8}	7.3×10^{8}	5.45×10^{8}	6.4×10^{8}

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

[a] Testing performed using the Advent infectivity assay.

8.6. Minimizing environmental contamination with genetically modified organisms (GMO)

The trial will be performed in accordance with the South African Genetically Modified Organisms Act 15 of 1997 (as amended). Approved SOPs will be followed to minimise dissemination of the recombinant vectored vaccine virus into the environment. GMO waste will be inactivated according to approved SOPs.

8.7. Control Vaccine

Participants who are allocated to the control groups will receive two injections (all Groups) of 0.9% Normal saline (0.9% NaCl) instead of ChAdOx1 nCoV-19.

Participants will be blinded as to which intervention they are receiving. A vaccine accountability log of IP and placebo (NaCl) will be maintained at each trial site.

8.8. Compliance with Trial Treatment

All vaccinations will be administered by the research team and recorded in the CRF. The study medication will be at no time in the possession of the participant and compliance will not, therefore, be an issue.

8.9. Accountability of the Trial Treatment

Accountability of the IP and placebo will be conducted in accordance with the relevant SOPs.

8.10. Concomitant Medication

As set out by the exclusion criteria, participants may not enter the study if they have received: any vaccine in the 30 days prior to enrolment or there is planned receipt of any other vaccine within 30 days of each vaccination, any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any chronic use (>14 days) of any immunosuppressant medication (except ARVs in group 3 participants) within 6 months prior to enrolment or if receipt is planned at any time during the study period (inhaled and topical steroids are permitted).

8.11. Provision of Treatment for Controls

If this vaccine is proven to be efficacious following analysis of the primary endpoint and if the DSMC agrees, participants allocated to placebo group may be offered the IP.

9. ASSESSMENT OF SAFETY

Safety will be assessed by the frequency, incidence and nature of AEs and SAEs arising during the study, from the time of randomization (Day 0 visit) onward.

9.1. Definitions

9.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a participant, which may occur during or after administration of an IP and does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including any clinically significant abnormal laboratory finding or change from baseline), symptom or disease temporally associated with the study intervention, whether or not considered related to the study intervention.

9.1.2. Adverse Reaction (AR)

An AR is any untoward or unintended response to an IP. This means that a causal relationship between the IP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by the reporting medical Investigator as having a reasonable suspected causal relationship to an IP (i.e. possibly, probably or definitely related to an IP) will qualify as AR.

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

9.1.3. Serious Adverse Event (SAE)

An SAE is an AE that results in any of the following outcomes, whether or not considered related to the study intervention.

Death

Life-threatening event (i.e., the participant was, in the view of the Investigator, at immediate risk of death from the event that occurred). This does not include an AE that, if it occurred in a more severe form, might have caused death.

Persistent or significant disability or incapacity (i.e., substantial disruption of one's ability to carry out normal life functions).

Hospitalisation or prolongation of existing hospitalisation, regardless of length of stay, even if it is a precautionary measure for continued observation. Hospitalisation (including inpatient or outpatient hospitalisation for an elective procedure) for a pre-existing condition that has not worsened unexpectedly does not constitute a serious AE.

An important medical event (that may not cause death, be life threatening, or require hospitalisation) that may, based upon appropriate medical judgment, jeopardise the participant and/or require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events

include allergic reaction requiring intensive treatment in an emergency room or clinic, blood dyscrasias, or convulsions that do not result in inpatient hospitalisation.

Congenital anomaly or birth defect.

9.1.4. Serious Adverse Reaction (SAR)

An AE that is both serious and, in the opinion of the reporting Investigator or Sponsors, believed to be possibly, probably or definitely due to an IP or any other study treatments, based on the information provided.

9.1.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB.

9.2. Expectedness

No IP related SAEs are expected in this study. All SARs will therefore be reported as SUSARs.

9.3. Foreseeable Adverse Reactions:

The foreseeable ARs following vaccination with ChAdOx1 nCoV-19 include injection site pain, tenderness, erythema, warmth, swelling, induration, pruritus, myalgia, arthralgia, headache, fatigue, fever, feverishness, chills, malaise and nausea. Participants will be advised to make immediate contact with the site for any solicited adverse that is Grade 3 or 4 that occurred within 7 days of vaccination, to ensure timeliness of it being reported as an SAE and to determine necessary management.

9.4. Adverse Events of Special Interest

Disease enhancement following vaccination with ChAdOx1 nCoV-19, as defined by international working groups, will be monitored. Severe COVID-19 disease will be defined using clinical criteria. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate, need for ventilatory support, imaging and blood test results, amongst other clinically relevant parameters.

9.5. Causality

For every AE, an assessment of the relationship of the event to the administration of the vaccine will be undertaken by the PI-delegated clinician. An interpretation of the causal relationship of the intervention to the AE in question will be made, based on the type of event; the relationship of the event to the time of vaccine administration; and the known biology of the vaccine therapy. Alternative causes of the AE, such as the natural history of pre-existing medical conditions, concomitant therapy, other risk factors and the temporal relationship of the event to vaccination will be considered and investigated. Causality assessment will take place during planned safety reviews, interim analyses (e.g. if a holding or stopping rule is activated) and at the final safety analysis, except for SAEs, which should be assigned by the reporting investigator, immediately, as described in SOP for Safety Reporting for CTIMPs.

Table 11: Guidelines for assessing the relationship of vaccine administration to an AE

0	**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
1	**Unlikely**	Unlikely temporal relationship to study product ***and*** Alternate aetiology likely (clinical state, environmental or other interventions) ***and*** Does not follow known typical or plausible pattern of response to study product.
2	**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
3	**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
4	**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

9.6. Reporting Procedures for All Adverse Events

All local and systemic AEs occurring in the 28 days following each vaccination observed by the Investigator or reported by the participant, whether or not attributed to study medication, will be recorded in paper or electronic diaries and entered onto the study database. All AEs that result in a participant's withdrawal from the study will be followed up until a satisfactory resolution occurs, or until a non-study related causality is assigned (if the participant consents to this). SAEs and Adverse Events of Special Interest will be collected throughout the entire trial period. All SAE reports will be submitted to HREC and SAHPRA regularly, as per current guidelines. A line list of all AEs will be submitted to HREC & SAHPRA as an appendix to annual progress report.

9.7. Assessment of severity

The severity laboratory adverse events will be assessed according to scales based on DAIDS AE Grading Version 2.1-July 2017 (Table 13) for adolescent adult study participants. Grading for local adverse events will be based on severity grading criteria indicated in Table 12.

Table 12: Severity grading criteria for local adverse events

Adverse Event	Grade	Intensity
Pain at injection site	1	Pain that is easily tolerated
	2	Pain that interferes with daily activity
	3	Pain that prevents daily activity
	4	A&E visit or hospitalization
Tenderness	1	Mild discomfort to touch
	2	Discomfort with movement
	3	Significant discomfort at rest
	4	A&E visit or hospitalization
Erythema at injection site*	1	2.5 - 5 cm
	2	5.1 - 10 cm
	3	>10 cm
	4	Necrosis or exfoliative dermatitis

Induration/Swelling at injection site	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 - 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
	4	Necrosis

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

Table 13: Severity grading criteria for select physical observations (Based on DAIDS Grading Table; Version 2.1 –July 2017

Vital signs	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 Potentially life threatening
	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C	≥ 38.6 to < 39.3°C	≥ 39.3 to < 40.0°C	≥ 40.0°C or ≥ 104.0°F
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social &	Muscle pain causing greater than minimal interference with usual social &	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions

	functional activities	functional activities		
Pain (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e g., CPAP, BPAP, intubation)

9.8. Reporting Procedures for Serious AEs

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately and notification deadlines respected. SAEs will be reported on the SAE forms to members of the study team within 24 hours of the Investigators becoming aware of their occurrence, as described in SOP Safety Reporting. Copies of all reports will be forwarded for review to the Principal Investigator in South Africa and the UK Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The DSMC will

be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMC will be notified immediately (within 24 hours) of the Investigators' being aware of their occurrence. SAEs assessed to be possibly, probably or definitely related to trial, or involving hospitalization or death of participant will be reported to the ethical committee(s), regulatory authority (SAHPRA) and UK chief investigator within 24 hours of investigator being aware of SAE. In addition to the expedited reporting above, the Investigator shall include all SAEs in the annual Development Safety Update Report (DSUR) report.

Grade 4 laboratory AEs should be reported as SAEs and under the category of outcome of an important medical event. A&E attendances should not routinely be reported as SAEs unless they meet the SAE definition described above.

Cases falling under the Hy's Law should be reported as SAEs. A Hy's Law Case is defined by FDA Guidance for Industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" (2009). Any study participant with an increase in Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin ≥2xULN, where no other reason can be found to explain the combination of these abnormal results, e.g., elevated serum alkaline phosphatase (ALP) indicating cholestasis, viral hepatitis A, B or C, another drug capable of causing the observed injury, amongst others.

9.9. Reporting Procedures for SUSARS

All other SUSARs will be reported by the investigator to the sponsor delegate (UK Chief investigator) and to the relevant Competent Authority and to the REC and other parties as applicable. Any additional relevant information for related SAEs and deaths will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

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

9.10. Development Safety Update Report

A Development Safety Update Report (DSUR) will be prepared annually, within 60 days of the anniversary of the first approval date from the regulatory authority for each IMP. The DSUR will be submitted by the national PI to the Competent Authority, Ethics Committee, and Sponsor.

9.11. Procedures to be followed in the event of abnormal findings

Eligibility for enrolment in the trial in terms of laboratory findings will be assessed by clinically

qualified staff. Abnormal clinical findings from medical history, examination or blood tests will be assessed as to their clinical significance throughout the trial. Laboratory AEs will be assessed using specific toxicity grading scales adapted from the DAIDS AE Grading Table Version 2.1 –July 2017 for Healthy Adult and Adolescent Participants. If a test is deemed clinically significant, it may be repeated, to ensure it is not a single occurrence. If a test remains clinically significant, the participant will be informed and appropriate 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.

9.12. Interim Reviews

The safety profile will be assessed on an on-going basis by the Investigators. The national PI and relevant site Investigators (as per the trial delegation logs) will also review safety issues and SAEs as they arise.

Interim safety reviews are planned monthly, and will include safety reviews (i) after group 1 participants have completed 14 day post dose 1 (i) and dose 2 (ii) visits, (iii) after group 3 participants have completed 14-days post dose 1, and once all participants in groups 1,2 and 3 have been enrolled.

Immunopathology data from pre-clinical studies will be assessed by the UK- CI, national PI and relevant investigators and the DSMC.

The DSMC will evaluate frequency of events, safety and efficacy data every 4-8 weeks and/or as required. The DSMC will make recommendations concerning the conduct, continuation or modification of the study.

9.13. Data Safety Monitoring Committee

A Data Safety Monitoring Committee (DSMC) has been appointed to oversee the UK trial, and have agreed to oversee the South African study as well. A South African senior scientist has been co-opted onto this international DSMC. The DSMC will:

a) periodically review and evaluate the accumulated study data for participant safety, study conduct, progress, and efficacy.

b) make recommendations concerning the continuation, modification, or termination of the trial.

There will be a minimum of three appropriately qualified committee members of whom one will be the designated chair. The DSMC will operate in accordance with the trial specific charter, which will be established before recruitment starts. In order to maintain continuity, the members of the DSMC overseeing the UK trial of the ChAdOx1-nCoV-19 vaccine (CoV001) will also be members of the DSMC for this trial. At least one African scientist will be added to the existing trial DSMC.

The chair of the DSMC may be contacted for advice and independent review by the Investigator or trial Sponsor in the following situations:

- Following any SAE deemed to be possibly, probably or definitively related to a study intervention.
- Any other situation where the Investigator or trial Sponsor feels independent advice or review is important.

The DSMC will review SAEs deemed possibly, probably or definitively related to study interventions. The DSMC will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMC has the power to place the study on hold if deemed necessary following a study intervention-related SAE.

9.14. Safety Group Holding Rules

Safety holding rules have been developed considering the fact that this trial will enroll people living with HIV, who have not previously been enrolled in a trial utilizing this IP.

Solicited AEs are those listed as foreseeable ARs, occurring within the first 7 days after vaccination (day of vaccination and six subsequent days). 'Unsolicited adverse events' are adverse events other than the foreseeable ARs occurring within the first 7 days, or any AEs occurring after the first 7 days after vaccination.

9.15. Holding rules

Group holding rules mentioned below will apply to all study Groups

- **Solicited local adverse events:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by 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 >72 hrs.

- **Solicited systemic adverse events:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by 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 >72 hrs.
- **Unsolicited adverse events:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 unsolicited adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >72 hrs.
- **Laboratory adverse event:**
  - If more than 25% of doses of the vaccine at a given time point (e.g. Day 0, Day 28) in a study group are followed by the same Grade 3 laboratory adverse event beginning within 2 days after vaccination (day of vaccination and one subsequent day) and persisting at Grade 3 for >72 hrs.
- **Any serious adverse event considered possibly, probably or definitely related to vaccination.**
  - If an SAE occurs in any one individual, which is possibly, probably or definitely related to vaccination this would trigger a holding rule. There are two exemptions from this rule, which would not activate a holding rule. These include:
    - COVID-19 related hospital admissions considered to be at least possibly related to ChAdOx1 nCoV-19 (e.g. if considered to be a clinical presentation of a disease enhancement episode). COVID-19 related SAEs will be regularly reviewed by the DSMB, and a single event will not trigger a holding rule.
    - SAEs reported under the Hy's Law requirement will not necessarily trigger a holding rule. These cases will also be reviewed by the DSMC

If any of the above holding rules are activated, then further vaccinations in any group will not occur until a safety review by the DSMC, study sponsor and the protocol Co-chairs has been conducted and it is deemed appropriate to restart dosing. The Regulatory Authority will be informed and a request to restart dosing with pertinent data will be submitted. The safety review will consider:

The relationship of the AE or SAE to the vaccine.

The relationship of the AE or SAE to the vaccine dose, or other possible causes of the event.

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) are discussed.

New, relevant safety information from ongoing research programs on the various components of the vaccine.

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

All vaccinated participants will be followed for safety until resolution or stabilisation (if determined to be chronic sequelae) of their AEs.

9.15.1. Individual stopping rules

In addition to the above stated holding rules, stopping rules for individual participants will apply (i.e., indications to withdraw individuals from further vaccinations). Study participants who present with at least one of the following stopping rules will be withdrawn from further vaccination in the study:

- **Local reactions:** Injection site ulceration, abscess or necrosis
- **Laboratory AEs:** the participant develops a Grade 3 laboratory AE considered possibly, probably or definitely related within 7 days after vaccination and persisting continuously at Grade 3 for 72hrs.
- **Systemic solicited adverse events:** the participant develops a Grade 3 systemic solicited AE considered possibly, probably or definitely related within 2 days after vaccination (day of vaccination and one subsequent day) and persisting continuously at Grade 3 for > 72hrs.
- **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 >72hrs.
    - the participant has a SAE considered possibly, probably or definitely related to vaccination.
    - the participant has an acute allergic reaction or anaphylactic shock following the administration of vaccine investigational product.
- **Any serious adverse event considered possibly, probably or definitely related to vaccination.**

If a participant has an acute respiratory illness (moderate or severe illness with or without fever) or a fever (oral temperature greater than 37.8°C) at the scheduled time of administration of investigational product/placebo, the participant will not be enrolled and will be withdrawn from the study.

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

In addition to these pre-defined criteria, the study can be put on hold upon advice of the DSMC, South African and UK Co-Chairs, Study Sponsor, regulatory authority, Ethical Committee(s), for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

10. STATISTICS

10.1. Description of Statistical Methods

A fully detailed statistical analysis plan will be developed and signed by the Co-chairs prior to any data analysis being conducted. For the efficacy endpoints, VE will be calculated as 1-RR and 95% confidence intervals estimated using the Clopper-Pearson exact method. In brief, the analysis will incorporate the following:

10.1.1 Efficacy endpoints:

Criteria for clinical diagnosis of incident COVID-19 *disease* in adults (Adapted from CEPI recommendations for standardisation COVID-19 vaccine efficacy trials).

Virologically confirmed COVID-19 clinical disease will be defined as an acute respiratory illness that is clinically consistent with COVID-19 based on the presence of criteria indicated in Table 5 and a positive SARS-CoV-2 specific reverse transcriptase polymerase chain reaction (RT-PCR). An expert external committee of at least two physicians will be convened to adjudicate on inclusion of clinical endpoints of incident COVID-19 cases for inclusion in the VE analyses.

10.2. Primary efficacy [objective] and endpoint in COVID-19-naive persons

The primary efficacy [objective] and endpoint include PCR positive symptomatic COVID-19 occurring in participants that were COVID-19 naïve at randomization who received two-doses of the planned study-allocated intervention, and where the first episode of COVID-19 occurred more than 14 days after the second dose of study-drug. COVID naïve will be defined as sero-negative at time of randomization based on a high sensitivity serology antibody targeted at the whole-length spike protein and receptor binding domain protein, and tested negative on nasal swab for SARS-CoV-2 by molecular detection. This analysis will include participants randomised to Group-1 being analysed together with Group-2 participants, all of whom will have received a two-dose schedule of study-intervention.

A sensitivity analysis will be conducted using a modified intention-to-treat (mITT) approach. This analysis will include COVID-19 naïve participants who received two doses of either the investigational product or placebo, regardless of whether it was the planned study-allocation intervention.

Only events that occur more than 14 days after vaccination will be included in mITT efficacy evaluations, to allow for exclusion of SARS-CoV-2 infections that may have occurred within 7 days of the 2nd dose and may have been asymptomatic prior to the anticipated optimal immune response after the second dose of vaccine. Vaccine efficacy (VE) will be calculated as (1 – RR) x 100%, where RR is the relative risk of symptomatic infection (ChADOx1 nCOV-19: placebo) and 95% confidence intervals will be presented.

Cumulative incidence of COVID-19 disease will be presented using the Kaplan-Meier method.Depending on the rate of accrual of endpoint cases meeting the primary-endpoint criteria in this study and phase II/III efficacy studies ChAdOx1 nCoV-19 that are currently underway in Brazil (ISRCTN89951424) and the United Kingdom (NCT: 04400838), it may be necessary to undertake a pooled analysis for the primary endpoint across the studies to provide an early readout of the efficacy of the ChAdOx1 nCoV-19. The study design and endpoint definitions across the studies are similar, and the categorisation of COVID-19 cases would be aligned. Should this be pursued, SAHPRA and the Ethics committees will be engaged to discuss the merits thereof. It is anticipated that blinding will be maintained on the part of the study-staff and the study-participants throughout this process on an interim pooled-analysis.

10.3. Secondary efficacy [objectives], endpoints and analyses, for overall population and based on COVID-19 sero-status at time of randomization

VE in preventing other virologically-confirmed COVID-19 clinical disease endpoints will include all cases occurring onward 14 days after a second dose; and from 21 days after a single dose, for the following endpoints:.

a. VE in preventing virologically-confirmed COVID-19 clinical disease irrespective of COVID-19 sero-status at randomization, and in those who were sero-positive at randomization.
b. VE in preventing PCR positive COVID-19 disease cases
c. VE in preventing moderate-severe confirmed COVID-19 disease.
d. VE in preventing severe confirmed COVID-19 disease.
e. VE in preventing LRTI associated with virologically-confirmed COVID-19 clinical disease
f. VE in preventing hospitalization due to virologically confirmed COVID-19 disease
g. VE in preventing all-cause LRTI (overall and stratified by hospitalization or not) irrespective of test result for SARS-COV-2.
h. VE using the Oxford Primary Outcome definition

10.4. Exploratory efficacy endpoints could include

a. VE in preventing death associated with virologically-confirmed COVID-19 clinical disease
b. VE in preventing virologically-confirmed COVID-19 disease or all-cause LRTI requiring supplemental oxygenation
c. VE in preventing virologically-confirmed COVID-19 disease or all-cause LRTI mechanical ventilation
d. VE in preventing virologically-confirmed COVID-19 disease or all-cause LRTI multi-organ dysfunction syndrome (MODS)
e. VE in preventing virologically-confirmed COVID-19 disease or all-cause LRTI all-cause mortality
f. VE in preventing asymptomatic SARS-CoV-2 infection (samples collected at scheduled study visits); i.e. no presence of any of the symptoms contributing to COVID-19 disease outcome, but virologically confirmed infection.
g. VE against sero-conversion suggestive of SARS-CoV-2 infection tested using a N-protein IgG assay.

10.4.1. Safety & Reactogenicity

Counts and percentages of each local and systemic solicited adverse reaction from diary cards, and all unsolicited AEs, and SAEs of special interest will be presented for each group.

10.4.2. Immunogenicity

Immune responses to be evaluated as per Table 8, Table 9, Table 10 include:

1. ELISA or Luminex assay (to be finalized based on current laboratory investigations) for whole spike protein and receptor binding domain.
2. ELISA or Luminex assay for N-protein IgG (to discriminate sero-conversion that is independent of SARS-CoV-2 proteins included in the vaccine. This assay is currently being developed and addresses an exploratory objective of the study.
3. Cell mediated immune response using an ELISPOT assay.
4. Th1 and TH2 cytokine profile using a Luminex assay.
5. Neutralization assays and Fc effector assays using pseudotyped and/or live virus assays

Currently a WHO COVID-19 serology working group (Solidarity II – COVID-19 Seroepidemiology) has established standard research sera (NIBSC code 20/130) and serum controls panel (NIBSC code 20/118) for harmonization of assays to be used across vaccine studies, and the detail of the proposed assays will be adapted per the latest development and recommendation by the WHO

serology working group.

Highly skewed ELISA data will be log-transformed prior to analysis. The geometric mean concentration and associated 95% confidence interval will be summarised for each group at each time point, by computing the anti-log of the mean difference of the log-transformed data. Neutralisation measurements will use an assay adapted from well-validated existing HIV-based pseudovirus neutralization assays using the pNL4–3.luc.R-E HIV construct with a SARS-CoV-2 spike protein. This assay is being developed and validated in collaboration with Dr David Montefiori, Duke University. Fc effector functionality, including antibody dependent cellular cytotoxicity, complement deposition, and phagocytosis will assess responses to spike trimer or the receptor binding domain

10.5. The Number of Participants

10.5.1. Sample size

Primary safety objective

Table 14 shows the probability of observing zero, at least one or at least two participants with an event among groups of size 25 and 50 for a range of true event probabilities. For example, if the true rate of a serious event is 0.01, there is a 77.8% chance that there will be no participants that experience this event in a group of 25 participants and a 22.2% chance of at least one participant who experiences the event.

Table 14: Calculated probability of observing zero, at least one or at least two participants with and event among groups of size 25 or 50 for a range of true event probabilities:

	Group size = 25			Group size = 50		
True event rate (%)	Zero participants with an event (%)	At least one participant with an event (%)	At least two participants with an event	Zero participants with an event	At least one participant with an event	At least two participants with an event
1	77.8	22.2	2.6	60.5	39.5	8.9
5	27.7	72.3	35.8	7.7	92.3	72.1
10	7.2	92.8	72.9	0.5	99.5	96.6
20	0.4	99.6	97.3	0	100	100
30	0	100	99.8	0	100	100

To estimate the true rate of a serious event, Exact Clopper-Pearson two-sided 95% confidence intervals (CIs) will be calculated. Table 15 lists calculated 95% CIs for the true rate of a serious event when 0, 1 or 2 participants observe events for a group of size 25 or 50

Table 15: Exact Clopper-Pearson 95% confidence intervals (CI) when 0,1, or 2 participants observe a serious event for a group size of 25 or 50

Observed number of participants with a serious event	95% CI for the true rate (%) of a serious event (group size = 25)	95% CI for the true rate (%) of a serious event (group size = 50)
0	(0, 13.7)	(0, 7.1)
1	(0.1, 20.4)	(0.1, 10.6)
2	(1, 26)	(0.5, 13.7)

Primary immunogenicity

The minimum detectable difference in response rates between 2 groups (group size =25) for 80% and 90% power is listed in Table 16.

Table 16: Minimum detectable difference in response rates between 2 groups calculated for various true response rates in the placebo group for groups size of 25 and statistical power of 80% and 90%.

True response rate in unvaccinated group (%)	True response rate in vaccinated group (%)	
	80% power	90% power
10	48.4	54.2
20	60.5	66.0
30	70.8	76.2
40	80.5	85.5
50	88.9	92.5

*Based on Fisher's exact test

Primary efficacy objective

Sample size calculations based on the total number of cases required to conclude with 80% power the lower limit of a two-sided 95% confidence interval for vaccine efficacy (VE, success criteria) is greater than 0% and 10% are shown in Table 17 for VE ranging from 60%-90% and attack rate in the unvaccinated population ranging from 5%-20%. Sample sizes are adjusted for a 10% loss to follow-up.

Table 17: Sample size for group 2 required to conclude with 80% power the lower limit of a two-sided 95% confidence interval for vaccine efficacy (VE) is greater than 0% and 10%.

Attack rate in unvaccinated participants (%)			1.5	2	2.5	3	3.5	4	5	10	15	20
Total cases (total cases in vaccinated group)	Success criteria	VE										
42 (12)	0%	60%	4447	3336	2669	2225	**1907**	1669	1336	669	445	336
28 (6)	0%	70%	3192	2394	1916	1596	1369	1198	958	480	320	240
17 (3)	0%	80%	2100	1576	1260	1052	900	789	632	316	212	158
12 (1)	0%	90%	1618	1214	972	809	694	607	487	245	163	123
57 (16)	10%	60%	6034	4525	3620	3018	2587	2263	1812	907	605	454
32 (7)	10%	70%	3649	2736	2189	1825	1565	1369	1096	549	367	276
19 (3)	10%	80%	2347	1760	1409	1174	1007	880	705	354	236	178
13 (1)	10%	90%	1752	1314	1052	876	752	658	527	265	176	134

Assuming a final total sample size in Group 2 of 1900 (950 per arm), the power to conclude the lower limit of a 95% confidence interval for VE is greater than 10% is listed below in for various assumed true VE and attack rates in the unvaccinated population.

Table 18: Calculated power to conclude the lower limit of a 95% confidence interval for VE is greater than 0% or 10% for a total sample size of 1900 (950 per arm).

Power (Exact method)			
VE (%)	Attack rate in unvaccinated (%)	Success Criteria	
		0%	10%
60	2	72.78	60.06
60	2.5	81.46	72.09
60	3.5	93.52	83.97
60	3	90.62	77.3
60	4	97.35	92.67
60	5	98.91	96.88
60	10	100	99.96
60	20	100	100
70	2	91.14	83.54
70	2.5	96.77	88.24
70	3.5	99.28	97.07
70	3	98.02	96.06
70	4	99.74	98.86
70	5	99.97	99.83
70	10	100	100
70	20	100	100

10.6. Procedure for Accounting for Missing, Unused, and Spurious Data.

All available data will be included in the analysis

10.7. Inclusion in Analysis

All vaccinated participants will be included in the analysis and will be analysed according to vaccine received.

10.8. Interim analysis

The independent DSMC will meet regularly to review safety data and will assess whether the assumptions underlying the sample size calculation are in line with the observed cases.

11. DATA MANAGEMENT

11.1. Data Handling

The national principal investigator will be responsible for all data that accrue from the trial.

All trial data including participant diary will be recorded directly into an Electronic Data Capture (EDC) system (REDCap) or onto a paper source document for later entry into EDC if direct entry is not available. This includes safety data, laboratory data and outcome data. Any additional information that needs recording but is not relevant for the CRF (such as signed consent forms etc.) will be recorded on a separate paper source document. All documents will be stored safely and securely in confidential conditions.

All adverse event data (both solicited and unsolicited) reported by the participant will be entered onto a participant's paper diary card for a maximum of 28 days following administration of the IP. The Diary provides a full audit trial of edits and will be reviewed at each review time-points indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF and followed to resolution, if there is a causal relationship to the IP, or to the end of the study if there is no causal relationship.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will only be included in password-protected trial electronic logs, which will be used for tracing and medical records and laboratory results and conducting surveillance calls as required. Personal identifiers will not be accessible by any person/ institution outside of immediate study team.

The EDC system (CRF data) uses a relational database (MySQL/ PostgreSQL/ REDCap) via a secure web

interface with data checks applied during data entry to ensure data quality. The database includes a complete suite of features which are compliant with GCP, EU and UK regulations and Sponsor security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The REDCap, MySQL and PostgreSQL database and the webserver will both be housed on secure servers maintained by the University of the Witwatersrand and RMPRU IT personal. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. The IT servers provide a stable, secure, well-maintained, and high capacity data storage environment. REDCap and OpenClinica are widely-used, powerful, reliable, well- supported systems. Access to the study's database will be restricted to the members of the study team by username and password.

11.2. Record Keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of participants. The South African national principal investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s), as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

All trial records will be stored for a minimum of 15 years after the end of the trial at a secure archiving facility. If participants consent to be contacted for future research, information about their consent form will be recorded, retained and stored securely and separately from the research data. If participants consent to have their samples stored and used in future research, information about their consent form will be recorded, retained and stored securely as per sample storage procedures and SOP.

11.3. Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the CRF. Source documents are original documents, data, and records from which the participant's CRF data are obtained. For this study, these will include, but are not limited to, participant consent form, blood results, community clinic and private general practitioner notes held by participant, laboratory records, diaries, medical records and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, adverse event data and details of vaccinations. All source data and participant CRFs will be stored

securely.

11.4. Data Protection

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

11.5. Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented.

11.6. Archiving

Trial data may be stored electronically on a secure server, and paper notes will be kept in a key-locked filing cabinet at the site. All essential documents will be retained for a minimum of 15 years after the trial has finished. The need to store study data for longer in relation to licensing of the vaccine will be subject to ongoing review.

General archiving procedures will be conducted in compliance to local SOP for Archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

12.1. Investigator procedures

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

12.2. Monitoring

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

12.3. 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 participant safety and study conduct. Significant protocol deviations will be listed in the end of study report.

12.4. Audit & inspection

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

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

GCP inspections may also be undertaken by the HREC or SAHPRA to ensure compliance with protocol and the National Health Act No 61 (as amended) and Guidelines in Good Clinical Practice for the conduct of trials with human participants in South Africa 2006, as amended. The Sponsor will assist in any inspections and will support the response to the HREC/ SAHPRA as part of the inspection procedure.

13. ETHICS AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigators will ensure that this study is conducted according to the principles of the current revision of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

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

13.3. Ethical and Regulatory Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC: University of the Witwatersrand, OxTREC, University of Cape Town, University of Stellenbosch), regulatory authorities (SAHPRA in South Africa, MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor and national principal investigator.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for

which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the participant (i.e. as an Urgent Safety Measure).

13.4. Participant Confidentiality

The study will comply with the Protection of Personal Information **Act**, No 4 of and relevant Data Protection Act, which require data to be de-identified as soon as it is practical to do so. The processing of 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), with the exception of informed consent forms and participant ID logs. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data. A separate confidential file containing identifiable information will be stored in a secured location in accordance with the current data protection legislation. Photographs taken of vaccination sites (if required, with the participant's written, informed consent) will not include the participant's face and will be identified by the date, trial code and participant's unique identifier. Once developed, photographs will be stored as confidential records, as above. This material may be shown to other professional staff, used for educational purposes, or included in a scientific publication.

If participants are diagnosed with COVID-19 during the course of the study then the study team will pass on their details to the local health protection team, if required, in line with the relevant notifiable disease legislation. Samples collected for the purposes of COVID-19 diagnosis might be sent to reference labs in South Africa alongside their personal data. This would be in line with the national guidance and policy for submitting samples for testing at reference labs.

14. FINANCING AND INSURANCE

14.1. Financing

The vaccine development and manufacture study is funded through UK Research and Innovations. The vaccine will be supplied free of charge to South African sites by UK chief collaborator.

Funding for the trial conduct will be finalized prior to trial initiation. National PI is in discussion with several stakeholders who may contribute to trial funding, including The Bill & Melinda Gates Foundation and South African Medical Research Council.

14.2. Insurance

The investigators have medical malpractice insurance. Trial-specific insurance has been obtained and

insurance certificates will be shared with regulatory and ethics committees and will be available at all sites prior to trial initiation. Clinical management of COVID-19 will be undertaken by public or private health care providers (participant's choice/ insurance dependent), and will be under relevant institution indemnity.

14.3. Compensation

Participants will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. Compensation rates will be aligned to those recommended by SAHPRA.

15. Publication Policy

South African investigators/collaborators and UK collaborators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study.

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

The IP has been developed by the University of Oxford and ownership of IP vests in the University of Oxford. Several UK investigators are applicants or co-inventors on previous patent filings or patents related to ChAdOx1 vaccines. The University of Oxford, which is partnered with the Oxford University Hospitals NHS Foundation Trust in the NIHR Oxford Biomedical Research Centre, is committed to the translational progress and commercial development of healthcare products potentially meeting medical and global health needs, and does and will work with commercial partners towards these goals.

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Appendix 1: Amendment history

Summary of protocol amendments: Version 1.0 to version 2.0 11th May 2020

Protocol Title: An adaptive phase I/IIa randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 2, 8th May 2020

Section	Amendment made	Justification
SA collaborators	Added Dr Alane Izu	Statistician at RMPRU. Provided sample size calculations for protocol, will oversee database development, data analysis
Inclusion criteria, trial population	Increased upper age limit to 65 years	The upper age limit of participants has been increased from 55 years to 65 years in line with HREC recommendation. Although co-morbid disease prevalence increases with increasing age, not all adults over 55 years are vulnerable and should be given the opportunity to partake in this trial, as long as inclusion and exclusion criteria are fulfilled.
Sample size	Group 2 has increased by 2150, from 550 to 2700. Group 2a= 550 (original group 2) **Group 2b= 2150 (additional)** Group 1 and 3 sample size remains 50. **TOTAL sample size = 2800**	Considering the unpredictability of the force of SARS-CoV-2 infection and the lower than anticipated attack rate for the primary-endpoint cases in the study being undertaken in the UK, the sample size for Group 2 (efficacy cohort) has been expanded from the 550 included in protocol version 1.0, dated 24th April 2020 to 2700 in protocol version 2.0, 8 h May 2020. Enrolling up to a total of 2,700 people without HIV in Group-2, will provide 80% power to detect at least a 60% vaccine efficacy (lower bound of 95%CI >0) with an attack rate of 2.5% in the placebo arm. Ongoing review of the number of COVID-19 cases accrued during the course of the study, may lend itself to enrolling smaller number of participants should the attack rate be higher than 2.5%.

Section	Amendment made	Justification
Table of groups, visit schedule table	Protocol amendment will not be required if group 2 participants receive 2 doses	Safety and immunogenicity data from the UK trial, COV001, and group 1 of this trial will be reviewed by the DSMC at least monthly. The DSMC will be tasked to make a decision, based on these results, regarding whether participants in Group 2 will receive one or two doses of IP. This decision will be communicated as a formal DSMC resolution communication to investigators, SAHPRA and WHREC. The option of the 2nd dose in group 2 has been built into the study design and events schedule. A protocol amendment would therefore not be necessary.
Table of groups, visit schedule table	Blood collection in PAXgene® Blood RNA tube added	Blood collection in PAXgene® Blood RNA tube has been added in line with COV001 protocol and at the advice of funders, BMGF. The PAXgene® Blood RNA tube assists in stabilisation of intracellular RNA, thereby improving accuracy and reproducibility of gene expression data.
Table of groups, visit schedule table	HbA1C added to screening blood	The HbA1C is a test done to identify glycated haemoglobin. Measurement of HbA1C gives a clear indication of the average blood glucose levels over the duration of the life of the red blood cell, which is 8-12 weeks. High HbA1C levels indicate poor blood glucose level over time, either in known diabetics or undiagnosed diabetics/ pre-diabetic conditions. Participants with high HbA1C levels will be referred to relevant medical teams for further assessment and management of diabetes or pre-diabetic conditions.
Visit schedule tables, synopsis, main protocol body	Added visit schedule table for group 2b	Group 2b is an extended efficacy cohort. Participants in Group 2b (HIV-uninfected adults) will have fewer scheduled visits and sample collections than participants in group 2a.
Exclusion criteria	Added: Use of any unproven registered and unregistered treatments for COVID-19	SAHPRA request.

Section	Amendment made	Justification
7.1 Schedule of attendance	Blood volume updated to include amended testing schedule for all groups	Group 1 (305ml) and Group 3 (315ml) and Group 2a (205ml) volumes increased by the addition of HbA1C and PAXgene tests. Group 2b participants will have 160ml collected.
7.3 Blood tests, nasal swabs/ saliva & urinaysis	Immunology blood test details added	SAHPRA request; details of immunology testing included.
8.6	GMO section updated	Amended in accordance with South African regulations.
9.6. Reporting procedures for all AEs	Added 'All SAE reports will be submitted to HREC and SAHPRA regularly, as per current guidelines. A line list of all AEs will be submitted to HREC and SAHRA as an appendix to annual progress report'	SAHPRA request. The applicant confirms its commitment to adhering to the South African safety reporting guidelines.
10.1 Description of Statistical methods	Expanded	SAHPRA request A complete statistical analysis plan will be developed for the trial.

Summary of protocol amendments: Version 2.0 to version 2.1 29th May 2020

Protocol Title: An adaptive phase I/IIa randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 2.1, 29th May 2020

Section	Amendment made	Justification
Title	Removed 'a' from Phase IIa	
Sample size adjustment	Reduced from 2800 to 2000 overall	The sample size has been calculated using 3.5% attack rate, instead of 2.5% attack rate. Other parameters used in sample size calculation remain unchanged (60% VE, success criteria 0%, 80% power)
Adjustment of group 2a and 2b	Group 2a reduced from 550 to 250 Group 2b reduced from 2150 to 1650	The UK COV001 trial (>1000 enrolled) and group 1 of this trial will contribute to the intensive immunogenicity analyses. Group 2a sample size has been reduced to 250
Schedule of events tables clarified	Full physical examinations at screening, vaccination 2 and illness visits. Targeted physical examinations at other visits. Pulse oximetry added to observation	Protocol schedule of events tables and visit details have been clarified, to include full physical examination at screening, vaccination and illness visits. Targeted examinations can be done at other visits Pulse oximetry added to physical observation to allow for adequate monitoring and clear classification of respiratory symptoms
Schedule of events table	HIV testing of HIV-negative participants at trial conclusion added	To assess possible differences in immunological responses in participants who sero-convert to HIV-positive during the trial participation
Timing of group 3 enrolment	Group 3 enrolment will either be in parallel with or will follow on from group 1 enrolment. Section 5 updated	More than 1000 participants have been enrolled into The UK's COV001 trial and will have had at least 6 weeks follow up prior to trial initiation of trial in South Africa. As of 28th May 2020, no significant vaccine-relates AEs or SAEs have been recorded in HIV-negative participants in the UK.
Screening window clarified	Screening window confirmed to be 14 days prior to vaccination.	Text portions of protocol (6.3.2 & 7.4.1) updated to ensure consistency (previously had 7 day window, not 14 days)
7.3. Blood tests, nasal swab/ saliva & urinalysis	Details of immunological assays have been added to the protocol	At reviewers' request
Clinical COVID-19 disease:	Added arthralgia, fatigue, nasal	As new research emerges, the clinical diagnostic criteria for COVID-19 is being

objectives, analysis	congestion, nausea, vomiting to clinical symptoms	amended. Protocol amended in line with symptoms being observed in COVID-19 patients globally.
Analysis according to accepted clinical risk/ ordinal scale added	WHO ordinal scale have been added to secondary objective analysis	Several organisations, including BMGF and WHO have developed a mortality risk index or ordinal scale for COVID-19 disease severity. Assessment of trial participant's potential disease will be assessed according to the WHO ordinal scale.
Intent to treat analysis modified	Amended to a modified ITT analysis. Participants will be randomised according to the treatment that they actually received, rather than what they were randomised to receive.	A modified intent-to treat analysis is currently the more accepted form of analysis of randomised controlled trials. A modified ITT analysis incorporates the benefits of improved external validity obtained in ITT analyses with improved internal validity obtained in PP analyses. It allows for analysis according to participant's actual experience/ vaccine received, rather than planned experience.

Summary of protocol amendments: Version 2.1 to version 3.0 30th June 2020

Protocol Title: An adaptive phase I/IIa randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 3.0, 30th June 2020

Section	Amendment made	Justification
Cover pages	Trial registration added	Registration with Clinicaltrials.gov and Pan African Clinical Trial Registry finalised and numbers added to protocol
	Sponsor updated	University of Oxford has confirmed role of overall sponsor for trial
	Sites added	Additional sites in Gauteng (PHRU Kliptown; SCTC) and W. Cape (CLII, FAMCRU) have been added to assist with rapid enrolment of participants.
	External monitor changed from SCT consulting to PPD	Added PPD, who will be doing the blinded monitoring, as per requirements outlined in BMGF grant agreement and monitoring capacity for increased sample size SCT will perform unblinded monitoring and provide regulatory support
Synopsis, group details tables	Sample size increased. Group 1 increased from 50 to 70 participants, and overall sample size increased from 2000 to 2020 participants	Enrolment was initiated on 24th June 2020, and 8 participants were enrolled daily on 24th, 25th & 26th June 2020. Six of the first 24 (25%) participants tested positive for SARS-CoV-2 on nasal swab at enrolment visit, which has led to higher than anticipated non-evaluable participants. An additional 20 participants will be enrolled into Group1 to ensure adequate evaluable participants in safety cohort.
	Nasal swab for SARS-CoV-2 PCR testing will be collected at screening visit in 96 hours prior to randomisation	Twenty-five percent of first 24 participants enrolled tested positive for SARS-CoV-2 at enrolment. In order to ensure that this asymptomatic/ pre-symptomatic COVID-19 disease is identified prior to vaccination visit, a nasal swab for SARS-CoV-2 PCR will be collected in the 96 hours prior to vaccination visit.
	Serological (IgG) testing at screening	Participants need to be seronegative at vaccination visit to fulfil efficacy endpoint. Addition of immunology blood sample to screening visit to assess prior infection with SARS-CoV-2 (already screening/ safety bloods collected at screening)
	Amended Screening process	A new, reasonably abridged screening informed consent form is being implemented, which will allow for all screening procedures, including data collection (demographics, medical &

		surgical history) and safety and screening bloods. Additionally, a nasal swab for SARS-COV-2 testing collected at screening visit has been added to reduce the possibility of enrolling SARS-CoV-2 infected participant. The previously-approved main ICF will be modified and signed at the enrolment (vaccination) visit. Implementation of screening ICF will avoid interested volunteers, who become screening failures based on SARS-CoV-2 positivity (currently 25%) having to read detailed ICF at screening visit.
Objectives	Disease severity grading amended	DSMC advised not to use the NEWS65 grading scale, but rather to utilise grading scale based on CEPI criteria
Inclusion & Exclusion criteria	Amended	Previous and current COVID-19 disease included as exclusion criteria. Chronic diseases clarified
Schedule of events	Vaccination window amended from day 28±3 days to day 28±7	Amended in line with UK trials of ChAdOx1 nCoV-19
	Adverse events grading scale	Protocol updated to utilise DAIDS table throughout.
Informed consent forms	New screening ICF implemented	New screening ICF implemented to cover screening procedures, including SARS-CoV-2 blood and nasal swab testing
	ICFs amended	HIV&Hep B ICF amended: will be signed at screening visit 'Main' ICF amended; removed screening procedures and will be signed at enrolment as 'Enrolment' ICF Sample storage ICF amended to reflect 25 years sample storage

Summary of protocol amendments: Version 3.0 to version 3.1 13th July 2020

Protocol Title: An adaptive phase I/IIa randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 3.1, 13th July 2020

Section	Amendment made	Justification
Protocol signature page	Added	Added at request of sponsor
SoE, exclusion criteria	COVID-19 serological testing at screening visit to exclude volunteers who have had previous infection has been removed	Recent FDA guidelines suggest not screening for past infection, as future vaccines for the following reasons: 'although establishing vaccine safety and efficacy in SARS-CoV-2 naïve individuals is critical, vaccine safety and COVID-19 outcomes in individuals with prior SARS-CoV-2 infection, which might have been asymptomatic, is also important to examine because re-vaccination screening for prior infection is unlikely to occur in practice with the deployment of licensed COVID-19 vaccines' Additionally, logistical constraints in the laboratories have hampered timely release of serology results.
Holding rules	Clarified	Protocol not clear on holding rules. DSMB suggested amendment.
Objectives	Objectives amended to reflect participants will be stratified by SARS-CoV-2 serological status	Amended in line with removal of screening serological testing and trial exclusion if seropositive at screening
Amendment history	Protocol amendment history added as appendix	Added at request of sponsor
Screening ICF	Screening procedure (blood for SARS-CoV-2 serology) and exclusion criteria amended.	Amended to reflect changes made to protocol.

Summary of protocol amendments: Version 3.1 to version 4.0 19th August 2020

Protocol Title: An adaptive phase I/II randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 4.0, 19th August 2020

Section	Amendment made	Justification
Cover page	Version update	Version update
Synopsis summary table of groups	Updated that Group 2 to receive two doses of study-intervention.	Phase I UK data indicate enhanced immunogenicity after two dose schedule.
Synopsis summary table of groups	Corrected window period for 2nd dose (28 days +-7 days)	Corrected to align to text.
Synopsis schedule 2b table	Corrected blood volume at V3 and clarified HLA done at V2. Also, edited to indicate only two dose schedule visits Visit windows corrected to align with visit numbers	Corrections to align to text and also to confirm two dose schedule visits.
Synopsis (and main text) Visit schedule 2a table	Edited to indicate only two dose schedule visits Visit windows corrected to align with visit numbers	Confirm two dose schedule visits
Objectives (Synopsis and main text Section 4.0)	Primary objective changed for endpoints occurring more than 14 days after 2nd dose	Decision to use a two-dose schedule based on enhanced immunogenicity.
Objectives (Synopsis and main text Section 4.0)	Endpoints occurring more than 21 days after first dose relegated to secondary objective	Decision to use a two-dose schedule based on enhanced immunogenicity.
Section 3.5	Data from Phase I UK study added.	Data informed dosing schedule and decision to pursue 2 dose schedule in the study.
Section 5.0 (Trial design)	Changes to confirm that two dose schedule being used	2-dsoe schedule was an option earlier on, and now implemented for Group 2 based on the Phase I data from the UK. SAPHRA and Ethics committee already notified.
Table 7	Updated that Group 2 to receive two doses of study-intervention.	Phase I UK data indicate enhanced immunogenicity after two dose schedule and DSMC concur with two dose schedule.
6.3.2	Clarification on timing on 2nd scheduled dose if participant develops COVID-19 prior to 2nd dose	Ensure 2nd dose only given when clinically stable and have shown adequate recovery from Covid-19.
7.3	Change “Immunology” to “genetics”	Correction

7.4.3.1	Updated to indicate to dose schedule to be used in Group 2	Phase I UK data indicate enhanced immunogenicity after two dose schedule and DSMC concur with two dose schedule.
8.4	Duration between vaccine removal from freezer and use amended from 1 hour to 6 hours	In line with recommendations from manufacturer
8.5	Update of most recent data from other studies	More than 9,000 now vaccinated in UK study
8.5	Detail on clinical strengths of different vaccine doses	Analysis of lot-lot clinical strengths and rational for change in dose range from 5.0 to 7.5 x10^9 vp on Advent qPCR assay.
8.5	Addition of information about batch consistency and amended dose range to account for maintaining consistency for K0011 batch	Batch K0011 was originally dosed on qPCR and from the CMO in Italy, However, additional assays suggest a higher dose is appropriate to maintain consistency with previous batches of vaccine and so this has been amended in the protocol and IB.
9.8	Update on reporting of SAEs. Addition of Grade 4 laboratory AEs and Hy's law SAEs	Clarification of reporting of expected AE from vaccine and SAEs in line with changes to sponsor protocol
10.2	Primary endpoint/objective changed to endpoints occurring more than 14 days after 2nd dose	Align endpoint with new 2 dose schedule for Group 2, based on UK Phase I data.
10.2	Clarified only participants receiving the planned dose of vaccine are eligible for primary endpoint analysis.	Appears that the latest batch of vaccine (Lot K0011) might have lower concentration per milliliter than initially analyzed for. Some participants (N=XX) have received vaccine from this lot, and may have been under-dosed. These participants will be informed of them having been possibly been under-dosed (without unblinding). For purpose of analyses, these participants remain eligible for the sensitivity and secondary objectives, but are excluded from the primary endpoint analysis.
10.2	Inclusion the possibility of being involved in a pooled analysis for the primary endpoint that will include data from the studies underway in Brazil and UK.	To get an early readout of the efficacy of the study, which will be of global benefit, it is proposed that should it be observed there is significant decline in Covid-19 endpoint cases across the three studies (SA, UK and Brazil), that results for the primary endpoint may be pooled. This will be done without unblinding of study staff or participants, so that the study can reach their individual powered endpoints.
10.3	Revision of secondary endpoints	Aligned with change to a two dose schedule, and efficacy endpoints following a single dose now being secondary objective.
17	Updated reference	Added reference of UK Phase I study

Summary of protocol amendments: Version 4.0 to version 4.1 18th September 2020

Protocol Title: An adaptive phase I/II randomised placebo- controlled study to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARS-CoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV

Protocol Number: ChAdOx1 nCoV-19_ZA_phI/II

Protocol version, date: Revised Protocol version 4.1, 30th September 2020

Section	Amendment made	Justification
Investigators	Carmen Briner replaced Erica Lazarus as PHRU Kliptown site principal investigator	Erica Lazarus on sabbatical. Carmen Briner approved by SAHPRA as site PI
Schedule of events tables	PAX gene testing removed from group 2b	PAX-gene testing only being done for Group 1, 2a and 3 participants
Schedule of events tables	Group 2b HLA test added to day 28 visit	Inadvertently omitted in previous SoE tables
Schedule of events tables	Amendment of day 56 visit: amended to be 28 days ±7 after dose 2	The aim of the day 56 visit is to collect immunology samples 28 days after receipt of both doses of vaccine. The timing of the day 56 visit should therefore be calculated in relation to the date of receipt of the 2nd dose of study vaccine. The window period for the day 56 visit is date of dose 2 + 28 days (±7). Visits conducted prior to 9th September 2020 which are in alignment with previous protocol will not be regarded as protocol deviations. Clarification to protocol sent to HREC & investigators on 9th Sept 2020
Sample size- group 3	Increased from 50 to 100 participants	Expect ~ one-third to be sero-positive for SARS-CoV-2, hence having 100 will allow for approx. 30 vaccinees being sero-negative
Secondary objective added: group 3 (HIV-infected) participants	To descriptively compare immune responses to ChAdOx1 nCoV-19 in people living with HIV to HIV-uninfected individuals, overall and stratified by COVID-19 sero-status at enrolment.	This trial is the first ChAdOx1 nCoV1-9 vaccine trial which includes people living with HIV. Comparison of immune response in HIV-negative and HIV-positive participants will support planning for future trials and programmatic vaccine implementation
8.2	Revision to the manufacture, packaging, and labelling	To update the manufacture, packaging and labelling relocation from Clinical Biomanufacturing Facility (CBF), University of Oxford to the following GMP facilities - Cobra

		Biologics Limited, Symbiosis Pharmaceutical Services Limited, Advent Societa' A Responsabilita Limitata, and Thermofisher Scientific
8.3	Revision to the storage conditions of the vaccine	To update the storage condition requirements per vial batch
8.4	Revision to administration of the vaccine	To update the vaccine administration section to include information on the vials (Batch 20482B)
8.5	Rationale for dose	To update the analytical comparability assessment of ChAdOx1 nCoV-19 (AZD1222) details since the previous version of the protocol.