Trial Title:	An adaptive phase I/II randomized placebo-controlled trial 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.
Study Reference:	ChAdOx1 nCoV-19_ZA_phI/II
Protocol Version:	South Africa version 6.0
Date:	ZA_15th January 2021
Trial registration:	Clinicaltrials.gov: NCT04444674; Pan African Clinical Trial Registry: PACTR202006922165132.

South African National Principal Investigator and Protocol Co-Chair:
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Protocol Co-Chair (UK): Prof Andrew Pollard
University of Oxford

Sponsor: University of Oxford

Funder: UK Research and Innovation (For Vaccine supply only)
Funding: The Bill and Melinda Gates Foundation
and South African Medical Research Council

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Funders	UK Research and Innovation (Vaccine supply) Clinical Trial: The Bill and Melinda Gates Foundation and South African Medical Research Council
External Monitor, SA	PPD SA (PTY) Ltd (blinded) The Woodlands Office Park, Building 15, Cnr Kelvin and Woodlands Drive, Woodmead, 2191, PO Box 37, Woodlands, 2080 Phone: 011 612 8600 Fax: 011 612 8700 Contacts: Nicolette Stott; Nicolette.stott@ppdi.com Kevin Shikanga, Kevin.Shikanga@ppdi.com Savi Chetty-Tulsee (Unblinded, regulatory) SCT consulting Bryanston Homesteads, Ben Road, Bryanston, 2191 Email: savi.sct@mweb.co.za

Contents

Table of tables

Investigator agreement

The principal investigator is responsible for ensuring that all study site personnel, including sub-investigators and other staff members, conduct this trial according to this protocol, Good Clinical Practice (GCP) and International Conference on Harmonization (ICF) guidelines, the Declaration of Helsinki and the pertinent country laws and regulations and to comply with its obligations, subject to ethical and safety considerations during and after the trial completion. The principal investigator also agrees not to disclose the information contained in this protocol or any results obtained from this trial without written authorization.

I have read and approve the protocol specified above and agree in its content:

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Signature: DocuSigned by: Shabir Madhi 1E5B1570B94F452...	Date: 1/19/2021
Role: Protocol co-chair, University of Oxford	Name: Andrew Pollard
Signature: DocuSigned by: Andrew Pollard 27CC5B27171D437...	Date: 1/19/2021
Role: VIDA/ RMPRU site Principal Investigator	Name: Anthonet Koen
Signature: DocuSigned by: Anthonet Koen 46C683D57BD3476...	Date: 1/19/2021
Role: Wits RHI Shandukani Research Centre Principal Investigator	Name: Lee Fairlie
Signature: DocuSigned by: Lee Fairlie 5532C86B99CA426...	Date: 1/19/2021
Role: Setshaba Research Centre Principal Investigator	Name: Mduduzi S.L. Masilela
Signature: DocuSigned by: Mduduzi Masilela 6CE7D56EAD3847C...	Date: 1/19/2021
Role: PHRU Kliptown Principal Investigator	Name: Carmen Briner
Signature: DocuSigned by: Carmen Briner A2ECFCE0D904430...	Date: 1/19/2021
Role: FAMCRU Principal Investigator	Name: Shaun Barnabas
Signature: DocuSigned by: Shaun L. Barnabas 6281F30D44094AE...	Date: 1/19/2021
Role: UCT CLII Principal Investigator	Name: Prof Keertan Dheda
Signature: DocuSigned by: keertan Dheda 36598CB810BA42F...	Date: 1/19/2021
Role: SCTC Principal Investigator	Name: Dr Qasim Bhorat
Signature: DocuSigned by: Qasim Bhorat 696269FC4D1A423...	Date: 1/19/2021

1. SYNOPSIS

Trial Title	An adaptive phase I/II randomized placebo-controlled trial 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
Trial Identifier	ChAdOx1 nCoV-19_ZA_phI/II
Trial Registration	Clinicaltrials.gov: NCT04444674; Pan African Clinical Trial Registry: PACTR202006922165132
National Principal investigator and Protocol Co-chair, South Africa	Professor Shabir A. Madhi
UK Protocol Co-chair	Professor Andrew Pollard

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Clinical Phase	I/II
Design	Double -blinded, randomised, placebo controlled, multi-centre
Population	Healthy adults aged 18-65 years, living with and without HIV
Planned Sample Size	**2070** (possible upward adjustment for efficacy endpoint)
Planned Trial Duration:	Regular visits from enrolment through to at least 12 months later.

Summary table of groups

Group #	Group description	Objective	Follow up	Treatment	Vaccination schedule
1 (n=70)	People without HIV (HIV-uninfected)	Intensive Safety and immunogenicity	Intensive	ChAdOx1 nCoV-19 5-7.5x1010 vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
2a (n=250) §	People without HIV (HIV-uninfected)	Safety, intensive immunogenicity and vaccine efficacy	Extended	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
2b (n=1650) §	People without HIV (HIV-uninfected)	Safety, immunogenicity and vaccine efficacy	Extended	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
3 (n=100)	People living with HIV (HIV-infected)	Intensive Safety and immunogenicity	Intensive	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	Prime-boost 2* doses, 4 weeks (21-35 days) apart

*Participants will receive 2 doses of the same injection (EITHER IP or placebo) as assigned at randomization.

§Numbers will be increased to supplement for corresponding number of individuals randomized prior to implementation of Version 3.0 of the protocol that tested positive for SARS-CoV-2 on PCR at time of randomization.

Following review of the initial safety/immunogenicity phase I trial conducted in the UK; COV0001 trial, and after review of the initial safety/ immunogenicity trial COV0001 by the DSMC; it was confirmed that Group 2 participants will receive 2 doses. SAHPRA and WHREC had been informed of this decision based on the earlier protocol requirements. Also, 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) was expanded from the 550 included in protocol version 1.0, dated 24th April 2020. This will involve enrolling up to a total of 1900 people in Group-2, which will provide 80% power to detect at least a 60% vaccine efficacy (lower bound of 95%CI >0) with an attack rate of 3.5% in the placebo arm. Ongoing review of the number of COVID-19 endpoint cases accrued during the course of the study, may lend itself to enrolling smaller number of participants should the attack rate be higher than 3.5%. The sample size for Group-1 has been increased to 70 to accommodate for the higher than anticipated infection rate with SARS-CoV-2 (6 of initial 24 randomized subjects in Group-1). Similarly, in anticipation of approximately one-third of Group-3 participants possibly being already infected with SARS-CoV-2, the sample size will be increased to 100 to have approximately 30 sero-negative vaccinees and placebo recipients enrolled into the study.

Visit schedule, group 1 and 3

Visit number	Screening	V1	V2	V3	V4	V5	V6*	V7*	V8*	V9*	V10	V11	COVID-19
Day #	-14 to -1	0 (Vax1)	3	7	14	28 (Vax2)	31	35	42	56	182	364	Illness
	Screening	D0	V1+ 3 days ±1; (day 2-4)	V1 +7 days ±2 (day 5-9)	V1+ 14 days ±3 (day 11-17)	Visit 1 + 28 days ±7 (day 21-35)	V5+3 days ±1	V5+7 days ±2	V5+14 days ±3	V5 +28 (±7)	D182 (±14)	D364 (±14 days)	As required $
Eligibility	X	X											
Consenting	X§	X¥											
Inclusion/ exclusion	X	X				X							
Contraindications	X	X				X							
Vital signs #	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X												X
Physical examination	X (full)	X	X	X	X	X (full)	X	X	X	X	X	X	X (full)
Vaccination		X				X							
Post-vaccination obs		X	X (deltoid)	X (deltoid)		X	X (deltoid)	X (deltoid)					
Diary cards provided		X				X							X (illness DC)
DC collected				X				X					
Safety bloods (FBC, U&E, LFT)	X		X	X		X		X		X			
Screening bloods (HBsAg, HIV, HbA1C)	X											X (HIV Gr 1)	
HIV Viral load and CD4 (Grp 3 only)	VL and CD4												
Immunology bloods***		E, PAX (15.0-20.0ml)	Cyt, PAX (15.0 -20.0l)		E & CMI (20-25ml)	E, N, PAX (20.0-25.0ml)		Cyt (10-15mls)	E & N & CMI (25-30ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X												
Urinalysis bHCG (women only)	X	(X)				X							
Nasal swab/ saliva	X (V1-96 hours)	X		X	X	X		X	X	X	X	X	X

• Visit 5 to Visit 9 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.
§ Screening informed consent form (ICF).
¥Full study participation informed consent form, if remain eligible after completion of screening procedures.
Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;
** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window
***Abbreviations for laboratory tests: E =Elisa; Cyt= Th1 and Th2 cytokine profile; N= neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay, PAX= PAXgenes.
Blood test summary:

- Screening: Safety bloods (Full Blood Count, FBC; Urea and Electrolytes, U&E; Liver Function tests, LFT); Screening bloods (HBsAg, HIV, Glycosylated hemoglobin; HbA1c), In group 3 only- CD4+ -lymphocyte count, CD4+ & VHIV-1 viral load, VL)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Safety bloods (FBC, U&E, LFT)
- Visit 4 Immunogenicity- Elisa & cell-mediated immunity
- Visit 5 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Visit 6 NIL
- Visit 7 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 8 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity
- Visit 9 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa
- Visit 10 Immunogenicity- Elisa
- Visit 11 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assays
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

Visit schedule, group 2a (first 250 participants)

Visit number	Screening	V1	V2	V3	V4	V5*	V6*	V7*	V8	V9	COVID-19
Day #	-14 to -1	0 (Vax1)	7	14	28 (Vax2)	35	42	56	182	364	Illness
	Screening	D0	V1 +7 days ±2 (day 5-9)	V1+ 14 days ±3 (day 11-17)	Visit 1 + 28 days ±7	V4+7 days ±2	V4+14 days ±3	V4 +28 (±7)	D182 (±14)	D364 (±14 days)	As required [$]
Eligibility	X	X									
Consenting	X[§]	X[¥]									
Inclusion/ exclusion	X	X			X						
Contraindications	X	X			X						
Vital signs [#]	X	X	X	X	X	X	X	X	X	X	X
Medical history	X										X
Physical examination	X (full)	X	X	X	X (full)	X	X	X	X	X	X (full)
Vaccination		X			X						
Post-vaccination obs		X	X (deltoid)		X	X (deltoid)					
Diary cards provided		X			X						X (illness DC)
DC collected			X			X					
Screening bloods (HBsAg, , HIV, HbA1C)	X									X (HIV)	
Immunology bloods***		E, PAX (15.0-20.0)	Cyt, PAX (15.0 -20.0ml)	E & CMI (20-25ml)	E, N, PAX (20.0-25.0ml)		E & N & CMI (25-30ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X										
Urinalysis bHCG (women only)	X	(X)			X						
Nasal swab/ saliva	X (V1-96 hours)	X	X	X	X	X	X	X	X	X	X

• Visit 5 to Visit 7 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.

[§] Screening informed consent form (ICF).

[¥] Full study participation informed consent form, if remain eligible after completion of screening procedures.

[#] Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window
***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay.

Blood test summary:

- Screening: Screening bloods (HBsAg, HIV, HBA1C)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Immunogenicity- Elisa & cell-mediated immunity assay
- Visit 4 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay, PAX- HLA
- Visit 5 Nil
- Visit 6 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity assay
- Visit 7 Immunogenicity- Elisa
- Visit 8 Immunogenicity- Elisa
- Visit 9 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Illness visit Immunogenicity- Elisa

[$] Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days

Visit schedule, group 2b (extended efficacy cohort; remaining 1650 participants)

Visit number	Screening	V1	V2	V3	V4	V5	V6	COVID-19
Day #	-14 to -1	0 (Vax1)	28 (Vax2)	42	56	182	364	Illness
	Screening	D0	Visit 1 + 28 days ±7	V2+14 days ±3	V2 +28 (±7)	D182 (±14)	D364 (±14 days)	As required [$]
Eligibility	X	X						
Consenting	X[§]	X[¥]						
Inclusion/ exclusion	X	X	X					
Contraindications	X	X	X					
Vital signs [#]	X	X	X	X	X	X	X	X
Medical history	X							X
Physical examination	X(full)	X	X (full)	X	X	X	X	X (full)
Vaccination		X	X					
Post vaccination Obs		X	X					
Diary cards provided		X	X					X (illness DC)
DC collected			X					
Screening bloods (HBsAg, HIV, HbA1C)	X						X (HIV)	
Immunology bloods***		E (15-20 ml)	E, N, HLA (20-25 ml)	E & N (15-20ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X							
Urinalysis bHCG (women only)	X	(X)	X					
Nasal swab/ saliva	X (V1-96 hours)	X	X	X	X	X	X	X

[§] Screening informed consent form (ICF).

[¥]Full study participation informed consent form, if remain eligible after completion of screening procedures.

*

[#] Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI=cell-mediated immunity assay.

Blood test summary:

- Screening: Screening bloods (HBsAg, HIV, HbA1C)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay, HLA
- Visit 3 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay
- Visit 4 Immunogenicity- Elisa,
- Visit 5 Immunogenicity- Elisa
- Visit 6 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

Objectives:

In adults without HIV (HIV-uninfected)

Primary objective:

To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in healthy HIV-uninfected adults.

Co-primary objective:

To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19, defined as virologically confirmed (PCR positive) COVID-19 disease, in participants that were COVID-19 naïve at time of randomization and who received two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose. "COVID-19 naïve" will be defined as sero-negative and tested negative for SARS-CoV-2 infection based on a high sensitivity serology antibody test and molecular detection testing of nasal swab, respectively

Secondary objective

To assess the immunogenicity of ChAdOx1 nCoV-19 in healthy HIV-uninfected adults

Details of objectives Groups 1 & 2 (HIV-uninfected):

Objective	**Objective details**	**Endpoint measures**
Primary Objective (Group 1 and Group 2)	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination; d) change from baseline for safety laboratory measures and; e) occurrence of serious adverse events e) occurrence of disease enhancement episodes

<table>
<tr>
<td>Co- Primary objective

(Group 2a and 2b; efficacy cohort)</td>
<td>To assess efficacy of the candidate ChAdOx1 nCoV-19 against mild to severe COVID-19</td>
<td>The primary efficacy [objective] and endpoint include PCR positive COVID-19 disease cases occurring in participants that were COVID-19 naïve at the time of randomization and who received at least two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose.
Virologically-confirmed COVID-19 clinical disease will be defined as an acute respiratory illness that is clinically consistent with COVID-19 based on presence of:
<table>
<tr><th>New onset systemic</th><th>Endpoint Definitions</th></tr>
<tr><td>Mild</td><td>Any one of:
• Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications)
• New onset cough
• ≥ 2 COVID-19 respiratory/non-respiratory symptoms, AND</td></tr>
<tr><td>Moderate</td><td>≥ 1 of:
• Fever (≥ 37.8°C) + any 2 COVID-19 symptoms for ≥ 3 days (need not be contiguous days)
• High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days)
• Any evidence of significant LRTI:
Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (beyond baseline)
Tachypnea: 20 to 29 breaths per minute at rest
SpO2: < 94% on room air
Abnormal chest x-ray/CT consistent with pneumonia or LRTI</td></tr>
<tr><td>Severe</td><td>≥ 1 of:
• Tachypnea: ≥ 30 breaths per minute at rest
• SpO2: < 92% on room air or PAO2/FiO2 < 300
• High flow oxygen therapy, CPAP, or NIV (eg, CPAP/BiPAP)
• Mechanical ventilation or ECMO
• One or more major organ system failure[a] (eg, cardiac/circulatory, pulmonary, renal, hepatic to be</td></tr>
</table>
</td>
</tr>
</table>

Secondary objectives (Group 2)	To assess the efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 of differing severity	All secondary VE analyses will be done for the overall population and stratified by COVID-19 serological status at baseline including all cases occurring onward from 14 days and 21 days after the first (or single) dose and >14 days after second dose. Secondary VE analyses will also include stratification to evaluate VE for COVID-19 due to the N501.V2 (also known as 20C/501.V2 or B.1.351 lineage) a. VE in preventing virologically-confirmed COVID-19 clinical disease irrespective of COVID-19 sero-status at randomization and stratified by serostatus at randomisation. b. VE in preventing virologically-confirmed COVID-19 clinical disease occurring more than 14 days after a second dose for the overall population and those that were sero-positive at baseline.. c. VE in preventing moderate-severe virologically 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. h. VE using Oxford Primary Outcome definition (PCR+ at least one symptom of fever > 37.8^{o}C, cough, shortness of breath, anosmia, aguesia). i. VE against N501Y.v2 variant of the SAR-CoV-2 virus
Secondary objective (Group 1 and Group 2)	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (sero-conversion rates) b) Interferon-gamma (IFN-γ) enzyme- linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.
Exploratory immunology:	To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain	a.Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis. b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain “baits” to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity.

<u>In adults living with HIV (HIV-infected)</u>

Primary co-objectives:

- To assess the safety of the candidate vaccine ChAdOx1 nCoV in adults living with HIV.
- To evaluate the immunogenicity of ChAdOx1 nCoV-19 after first and second doses of vaccine.

Details of objectives Group 3 (HIV-infected):

	Objective details	**Endpoint measures**
Primary objective	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 in people living with HIV	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination; d) change from baseline for safety laboratory measures and; e) occurrence of serious adverse events e) occurrence of disease enhancement episodes
Co-primary objective	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19 in people living with HIV after one and two doses of vaccine	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.

Secondary objective	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.	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.
Exploratory immunology	To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain	a. Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis. b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain “baits” to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity.

Formulation Liquid

Investigational products

- ChAdOx1 nCoV-19, a non-replicating simian adenoviral vector expressing the spike (S) protein of SARS-CoV-2 (investigational product, IP)
- Normal saline, NaCl 0.9% as placebo

Route of Administration Intramuscularly (IM) into the deltoid region of the non-dominant arm

Dose per Administration ChAdOx1 nCoV-19 5-7.5x10^{10} vp

2. ABBREVIATIONS

AdHu	Human adenovirus
AdHu5	Human adenovirus serotype 5
AE	Adverse event
AID	Autoimmune Disease
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine, Oxford
CBF	Clinical Bio manufacturing Facility
CEF	Chick embryo fibroblast
ChAd63	Chimpanzee adenovirus 63
CI	Confidence interval
COP	Code of Practice
CRF	Case Report Form or Clinical Research Facility
CS or CSP	Circumsporozoite protein
CTRG	Clinical Trials & Research Governance Office, Oxford University
CTL	Cytotoxic T Lymphocyte
DSUR	Development Safety Update Report
ELISPOT	Enzyme-linked immunospot
GCP	Good Clinical Practice
GMO	Genetically modified organism
GMT	Geometric Mean Titre
GP	General Practitioner
GSK	GlaxoSmithKline
HCG	Human Chorionic Gonadotrophin
HBV	Hepatitis B virus
HEK	Human embryonic kidney
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRA	Health Research Authority
HREC	Human Research Ethics Committee
HTLV	Human T-Lymphotrophic Virus
IB	Investigator Brochure
ICH	*International Conference on Harmonisation*
ICMJE	*International Committee of Medical Journal Editors*
ICS	*Intracellular Cytokine Staining*
IDT	Impfstoffwerk Dessau-Tornau Biologika GmbH
ID	Intradermal
IFNγ	Interferon gamma
IM	Intramuscular
IMP	Investigational Medicinal Product
IMP-D	Investigational Medicinal Product Dossier
IP	Investigational Product
IV	Intravenous
LSOC	Local safety oversight clinician
ME-TRAP	Multiple epitopes and thrombospondin related adhesion protein
MVA	Modified vaccinia virus Ankara

NANP	N-acetylneuraminic acid phosphatase
NHLS	National Health Laboratory Service
NICD	National Institute for Communicable Diseases
PBMC	*Peripheral blood mononuclear cell*
Pb	*Plasmodium Berghei*
PCR	Polymerase chain reaction
PI	Principal Investigator
pfu	Plaque forming unit
QP	Qualified Person
qPCR	Quantitative polymerase chain reaction
QS21	*Quillaja saponaria* saponin molecule
REC	Research Ethics Committee
SAE	Serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SC	Subcutaneous
SmPc	Summary of Product characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
µg	microgram
vp	viral particle
VV	viral vector
WHO	World Health Organization

3. BACKGROUND AND RATIONALE

3.1. Background

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV [1]. The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus [2]. COVID-19 is the illness caused by SARS-CoV-2. By January 2020 there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARS-CoV-2 rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020. As of 15th January 2021 , over 93 million cases have been reported with more than 2.0 million deaths globally (Worldometers.info).

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors [3]. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus* and it uses the angiotensin-converting enzyme 2 (ACE2) as the entry receptor [4]. It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

The spike protein is a type I, trimeric, transmembrane glycoprotein located at the surface of the viral envelope of CoVs, which can be divided into two functional subunits: the N-terminal S1 and the C-terminal S2. S1 and S2 are responsible for cellular receptor binding via the receptor binding domain (RBD) and fusion of virus and cell membranes respectively, thereby mediating the entry of SARS-CoV-2 into target cells.[3] Neutralizing antibodies to SARS-CoV-2 are widely assumed to be correlated with recovery from infection, and the use of passively infused convalescent sera is being assessed for treatment of COVID-19. Such antibodies may protect from infection, as in vitro studies showed that cross-reactive SARS-CoV-1 antibodies prevented SARS-CoV-2 infection. The roles of S in receptor binding and membrane fusion, and the fact that it is the main target for neutralising antibodies, makes it an ideal target for vaccine and antiviral development. Furthermore, the potential of spike antibodies to mediate Fc effector functions has not been examined in SARS-CoV-2 vaccines,

nor extensively in any related coronaviruses including SARS-CoV-1. Fc effector function is protective against Ebola and HIV as well as against respiratory diseases such as tuberculosis and Influenza (Saphire, et al., 2018; Lu, et al., 2016; Su, et al., 2019; Vanderven and Kent, 2020).

A novel SARS-CoV-2 variant known as 501Y.V2 has been identified in South Africa and is responsible for its evolution in SA, and now responsible for 80-90% of COVID-19 cases identified during the second wave. The SARS-CoV-19 501Y.V2 variant is approximately 53% more transmissible than earlier variants of the virus.

In addition, SA has three additional mutations of the RBD, including the E484K mutation and mutations of the RBD loop protein. Testing of convalescent sera indicate that there is more than a 10-fold reduction in neutralising antibody activity to variant with these mutations. Hence, seems to be an immuno-dominant component for neutralising antibody, and possible that could affect vaccine induced immunity and efficacy (Greaney et al., 2021; Pearson et al. 2021; Voloch et al. 2020).

ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigen of the SARS CoV-2 (nCoV-19), with a leading tissue plasminogen activator (tPA) signal sequence. ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for the Spike protein from genome sequence accession GenBank: MN908947. The tPA leader sequence has been shown to be beneficial in enhancing immunogenicity of another ChAdOx1 vectored CoV vaccine (ChAdOx1 MERS) [5].

3.2. Pre-Clinical Studies

3.2.1. Immunogenicity (Jenner Institute, unpublished)

Mice (balb/c and CD-1) were immunised with ChAdOx1 expressing SARS-CoV-2 Spike protein or green fluorescent protein (GFP). Spleens were harvested for assessment of IFY ELISpot responses and serum samples were taken for assessments of S1 and S2 antibody responses on ELISA at 9 or 10 days post vaccination. The results of this study show that a single dose of ChAdOx1 nCoV was immunogenic in mice.

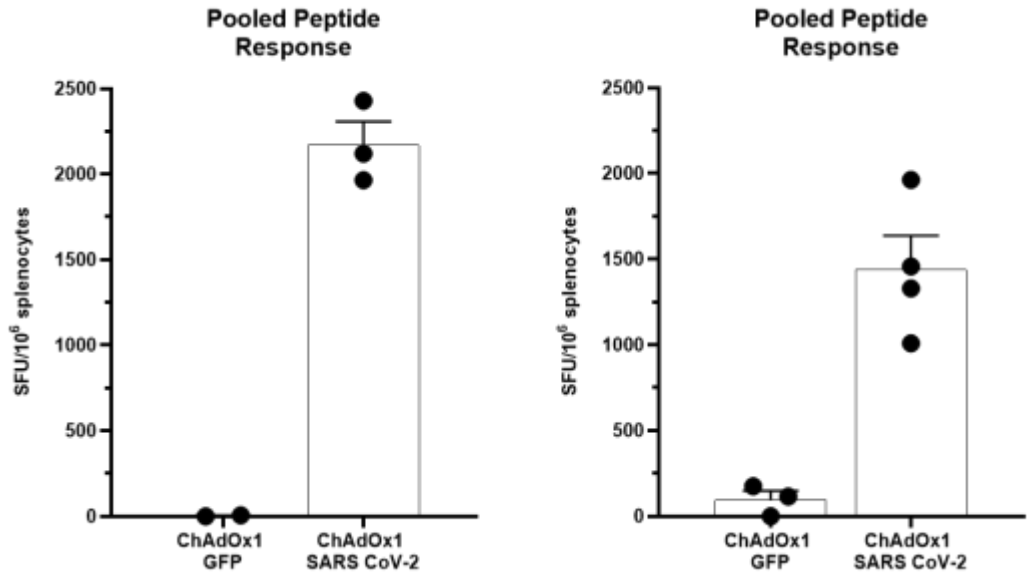

Figure 1. Summed splenic IFN-γ ELISpot responses of BALB/c (left panel) and CD-1 (right panel) mice, in response to peptides spanning the spike protein from SARS-CoV-2, nine or ten days post vaccination, with 1.7 × 10^{10} viral particles (vp) ChAdOx1 nCoV-19 or 8 × 10^{9} vp ChAdOx1 GFP. Mean with SEM are depicted.

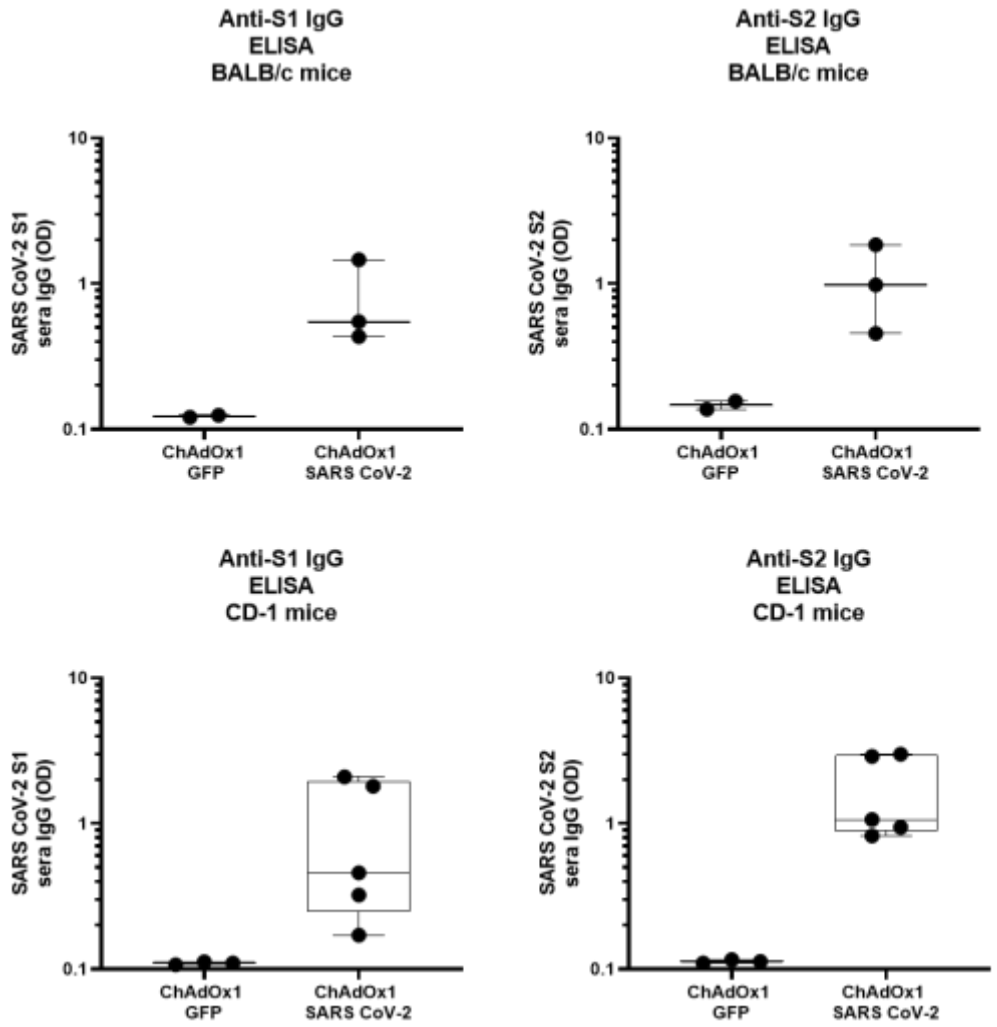

Figure 2. Box and whisker plot of the optical densities following ELISA analysis of BALB/C mouse sera (Top panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike nine or ten days post vaccination, with 1.7×10^{10} vp ChAdOx1 nCoV-19 or 8×10^{9} vp ChAdOx1 GFP. Box and whisker plots of the optical densities following ELISA analysis of CD-1 mouse sera (Bottom panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike.

3.2.2. Efficacy

Pre-clinical efficacy studies of ChAdOx1 nCoV-19 in ferrets and non-human primates are underway. Results will be included in an updated Investigator's Brochure when available.

3.3. Antibody Dependent Enhancement

Safety concerns around the use of full length coronavirus Spike glycoproteins and other viral antigens(nucleoprotein) as a vaccine antigen have been raised following historical and limited reports

of immunopathology and antibody dependent enhancement (ADE) reported in vitro and post SARS-CoV challenge in mice, ferrets and non-human primates immunised with whole SARS-CoV inactivated or full-length S protein based vaccines, including a study using Modified Vaccinia Ankara as a vector [6-8]. To date, there has been one report of lung immunopathology following MERS-CoV challenge in mice immunised with an inactivated MERS-CoV candidate vaccine [9]. However, in preclinical studies of ChAdOx1 immunisation and MERS-CoV challenge, no ADE was observed in hDPP4 transgenic mice, dromedary camels or non-human primates (van Doremalen et al, manuscript submitted) [10, 11].

The risks of inducing lung immunopathology in the event of COVID-19 following ChAdOx1 nCoV-19 vaccination are unknown. Challenge studies on ferrets and NHPs are underway and these pre-clinical studies will report on presence or absence of lung pathology. Results will be reviewed as soon as they emerge and will inform discussions on risk/benefit to participants receiving the Investigational Medical Product (IMP). All pathology data arising from challenge studies of other SARS-CoV-2 vaccine candidates will also be taken into account.

3.4. Previous clinical experience

The phase I/II study in health adults in the UK, initiated in late April 2020 is the first-in-human study employing ChAdOx1 nCoV-19, and as of mid-June 2020 had enrolled more than 7000 participants. Furthermore, ChAdOx1 vectored vaccines expressing different inserts have previously been used in over 320 healthy participants taking part in clinical trials conducted by or in partnership with the University of Oxford in the UK, Switzerland Uganda and Saudi Arabia (Table 1, Table 2). Most importantly, a ChAdOx1 vectored vaccine expressing the full-length Spike protein from another Betacoronavirus, MERS-CoV, has been given to 31 participants to date as part of MERS001 and MERS002 trials. ChAdOx1 MERS was given at doses ranging from $5x10^9$ vp to $5x10^{10}$ vp (table 2) with no serious adverse reactions reported. Further safety and immunogenicity results on ChAdOx1 MERS can be found on the Investigator's Brochure for ChAdOx1 nCoV-19 for reference.

Clinical trials of ChAdOx1 vectored vaccines encoding antigens for Influenza (fusion protein NP+M1), Tuberculosis (85A), Prostate Cancer (5T4), Malaria (LS2), Chikungunya (structural polyprotein), Zika (prM and E), MERS-CoV (full-length Spike protein) and Meningitis B are listed below.

None of the below mentioned clinical trials reported serious adverse events associated with the administration of ChAdOx1, which was shown to have a good safety profile.

Table 1: Clinical experience with ChAdOx1 viral vector vaccines.

Country	Trial	Vaccine	Age	Route	Dose	Number of Participants (Received ChAdOx1)	Publication / Registration Number
UK	FLU004	ChAdOx1 NP+M1	18-50	IM	$5x10^8$ vp	3	Antrobus et al, 2014. Molecular Therapy. DOI: 10.1038/mt.2013.284 [12]
					$5x10^9$ vp	3	
					$2.5x10^{10}$ vp	3	
					$5x10^{10}$ vp	6	
UK	FLU005	ChAdOx1 NP+M1 MVA NP+M1 (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	Coughlan et al, 2018. EBioMedicine DOI: 10.1016/j.ebiom.2018.02.011 DOI: 10.1016/j.ebiom.2018.05.001 [13]
		ChAdOx1 NP+M1 MVA NP+M1 (week 52)	18-50	IM	$2.5x10^{10}$ vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 52)	18-50	IM	$2.5x10^{10}$ vp	9	
		ChAdOx1 NP+M1	>50	IM	$2.5x10^{10}$ vp	12	
		ChAdOx1 NP+M1 MVA NP+M1 (week 8)	>50	IM	$2.5x10^{10}$ vp	12	

Country	Trial	Vaccine	Age	Route	Dose	Number of Participants (Received ChAdOx1)	Publication / Registration Number
UK	TB034	ChAdOx1 85A	18-50	IM	$5x10^9$ vp	6	Wilkie et al, 2020 Vaccine DOI: 10.1016/j.vaccine.2019.10.102 [14]
					$2.5x10^{10}$ vp	12	
		ChAdOx1 85A MVA85A (week 8)	18-50	IM	$2.5x10^{10}$ vp	12	
		ChAdOx1 85A (x2, 4weeks apart) MVA85A (at 4 months)	18-50	IM	$2.5x10^{10}$ vp	12	
Switzerland	TB039 (ongoing)	ChAdOx1 85A	18-55	Aerosol	$1x10^9$ vp	3	Clinicaltrials.gov: NCT04121494
				Aerosol	$5x10^9$ vp	3	
				Aerosol	$1x10^{10}$ vp	11	
				Aerosol/IM	$1x10^{10}$ vp	15	
Uganda	TB042 (ongoing)	ChAdOx1 85A	18-49	IM	$5x10^9$ vp	6	Clinicaltrials.gov: NCT03681860
					$2.5 x10^{10}$	6	
UK	VANCE01	ChAdOx1.5T4 MVA.5T4	18 – 75	IM	$2.5x10^{10}$ vp	34	Clinicaltrials.gov: NCT02390063

Country	Trial	Vaccine	Age	Route	Dose	Number of Participants (Received ChAdOx1)	Publication / Registration Number
UK	ADVANCE (ongoing)	ChAdOx1.5T4 MVA.5T4	≥18	IM	$2.5x10^{10}$ vp	23 (as of Feb 20)	Clinicaltrials.gov: NCT03815942
UK	VAC067	ChAdOx1 LS2	18-45	IM	$5x10^{9}$ vp	3	Clinicaltrials.gov: NCT03203421
					$2.5x10^{10}$ vp	10	
UK	VAMBOX	ChAdOx1 MenB.1	18-50	IM	$2.5x10^{10}$ vp	3	ISRCTN46336916
					$5x10^{10}$ vp	26	
UK	CHIK001	ChAdOx1 Chik	18-50	IM	$5x10^{9}$ vp	6	Clinicaltrials.gov: NCT03590392 DOI: https://doi.org/10.4269/ajtmh.abstract2019 Abstract #59, page 19.
					$2.5x10^{10}$ vp	9	
					$5x10^{10}$ vp	9	
UK	ZIKA001 (ongoing)	ChAdOx1 Zika	18-50	IM	$5x10^{9}$ vp	6	Clinicaltrials.gov: NCT04015648
					$2.5x10^{10}$ vp	3 (as of Feb 20)	
					$5x10^{10}$ vp	-	

Table 2: Clinical experience with ChAdOx1 MERS vaccine

Country	Trial	Vaccine	Age	Route	Dose	Number of Participants (Received ChAdOx1)	Publication / Registration Number
UK	MERS001 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ vp	6	Clinicaltrials.gov: NCT03399578 DOI: https://doi.org/10.4269/ajtmh.abstract2018 Abstract#973, page 305. Folegatti et.al. 2020, Lancet Infect.Dis, *In press*.
					$2.5x10^{10}$ vp	9	
					$5x10^{10}$ vp	9	
					$2.5x10^{10}$ vp (homologous prime-boost)	3	
Saudi Arabia	MERS002 (ongoing)	ChAdOx1 MERS	18-50	IM	$5x10^9$ vp	4	Clinicaltrials.gov: NCT04170829
					$2.5x10^{10}$ vp	3	
					$5x10^{10}$ vp	-	

3.5. Rationale

The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Containment measures have failed to stop the global spread of virus. There are currently no specific treatments available against COVID-19 and accelerated vaccine development is urgently needed. South Africa has currently had over 767,679 cases and 20,903 deaths. There was a peak in July 2020, followed three months of lower rates, however, rate has increased over the last 3 weeks. (Wordometer.info). Recent modelling data indicates that globally there are likely to be 3-4 waves of COVID-19 outbreaks, possibly extending through to 2022.

Live attenuated viruses have historically been among the most immunogenic platforms available, as they have the capacity to present multiple antigens across the viral life cycle in their native conformations. However, manufacturing live-attenuated viruses requires complex containment and biosafety measures. Furthermore, live-attenuated viruses carry the risks of inadequate attenuation causing disseminated disease, particularly in immunocompromised hosts. Given that severe disease and fatal COVID-19 disproportionally affect older adults with co-morbidities, making a live-attenuated virus vaccine is a less viable option. Replication competent viral vectors could pose a similar threat for disseminated disease in the immuno-suppressed. Replication deficient vectors, however, avoid that risk while maintaining the advantages of native antigen presentation, elicitation of T cell immunity and the ability to express multiple antigens [15]. Subunit vaccines usually require the use of adjuvants and whilst DNA and RNA vaccines can offer manufacturing advantages, they are often poorly immunogenic requiring multiple doses, which is highly undesirable in the context of a pandemic.

Chimpanzee adenovirus vaccine vectors have been safely administered to thousands of people using a wide range of infectious disease targets. ChAdOx1 vectored vaccines have been given to over 320 participants with no safety concerns and have been shown to be highly immunogenic at single dose administration. Of relevance, a single dose of a ChAdOx1 vectored vaccine expressing full-length spike protein from another betacoronavirus (MERS-CoV) has shown to induce neutralising antibodies in recent clinical trials (Folegatti et. Al. 2020. Lancet Infect Dis, In press).

A Phase I single-blind, randomised controlled trial in the UK of ChAdOx1 nCoV-19 enrolled healthy adults aged 18–55 years with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms, who were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a dose of 5×10^{10} viral particles or MenACWY as a single intramuscular injection. Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise. There were no serious adverse events related to ChAdOx1 nCoV-19. In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856 spot-forming cells per million peripheral blood mononuclear

cells, IQR 493–1802; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127), and were boosted following a second dose (639 EU, 360–792; n=10). Neutralising antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in MNA80 and in 35 (100%) participants when measured in PRNT50. After a booster dose, all participants had neutralising activity (nine of nine in MNA80 at day 42 and ten of ten in Marburg VN on day 56). Neutralising antibody responses correlated strongly with antibody levels measured by ELISA (R^2=0·67 by Marburg VN; p<0·001).[16] These data support the decision to pursue a two dose schedule for evaluation of efficacy of the vaccine candidate. Hence, this protocol has been adapted as such, with all Group now assigned to receive either two doses of ChAdOx1 nCoV-19 or placebo (Folegatti et al, Lancet 2020).

The trial to be conducted in South Africa will enroll adults living without and with HIV to assess safety, immunogenicity and efficacy two doses of ChAdOx1-nCoV-19. The South Africa study on ChAdOx1-nCoV-19 (Group 1 enrolment) was initiated following review by the Data and Safety Monitoring Committee (which oversees multiple ChAdOx1 nCoV-19 including the UK, South African and a planned study in Kenya) of the initial safety cohort (n=50) that will be enrolled in the UK. Enrolment into Group-1 of the study in South Africa occurred in tandem with opening of enrolment of the expanded immunogenicity and "efficacy-cohort" in the UK.

Recent guidelines from the Food and Drug Administration on conduct of COVID-19 vaccine trials recommend that "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. Therefore, COVID-19 vaccine trials need not screen for or exclude participants with history or laboratory evidence of prior SARS-CoV-2 infection. However, individuals with acute COVID-19 (or other acute infectious illness) should be excluded from COVID-19 vaccine trials".[17]

4. OBJECTIVES AND ENDPOINTS

In adults without HIV (HIV-uninfected)

Primary objective:

To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in healthy HIV-uninfected adults.

Co-primary objective:

To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19, defined as virologically confirmed (PCR positive) COVID-19 disease, in participants that were COVID-19 naïve at the time of randomization and who received two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose. "COVID-19 naïve" will be defined as sero-negative and tested negative for SARS-CoV-2 infection, based on a high sensitivity serology antibody

test and molecular detection testing of nasal swab, respectively.

Secondary objective

To assess the immunogenicity of ChAdOx1 nCoV-19 in healthy HIV-uninfected adults

Table 3: Details of objectives Groups 1 & 2 (HIV-uninfected):

Objective	**Objective details**	**Endpoint measures**
Primary Objective (Group 1 and Group 2 a and b)	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination; d) change from baseline for safety laboratory measures and; e) occurrence of serious adverse events e) occurrence of disease enhancement episodes
Co- Primary objective (Group 2a and 2b; efficacy cohort)	To assess efficacy of the candidate ChAdOx1 nCoV-19 against all-severity COVID-19	The **primary efficacy [objective] and endpoint** include PCR positive COVID-19 disease cases occurring in participants that were COVID-19 naïve at randomization and who received two doses of ChAdOx1 nCoV-19 or placebo. Events will be included if they occurred more than 14 days after the booster dose. Virologically-confirmed COVID-19 clinical disease will be defined as an acute respiratory illness that is clinically consistent with COVID-19 based on presence of criteria indicated in Table 4 and Table 5 **AND** a positive SARS-CoV-2 specific reverse transcriptase polymerase chain reaction (RT-PCR)

Secondary efficacy [objectives], endpoints	To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 of differing severity	**Secondary efficacy [objectives], endpoints** in for the overall population and stratified by COVID-19 serological status at randomisation including all cases occurring onward from 14 days and 21 days after the first (or single) dose and >14 days after second dose: Secondary VE analyses will also include stratification to evaluate VE for COVID-19 due to the N501.V2 (also known as 20C/501.V2 or B.1.351 lineage) a. VE in preventing virologically-confirmed COVID-19 clinical disease irrespective of COVID-19 sero-status at randomization and stratified by serostatus at randomisation. b. VE in preventing virologically-confirmed COVID-19 clinical disease occurring more than 14 days after a second dose for the overall population and those that were sero-positive at baseline. c. VE in preventing PCR positive COVID-19 disease cases. d. VE in preventing severe confirmed COVID-19 disease. e. VE in preventing virologically-confirmed moderate-severe COVID-19 clinical disease. f. VE in preventing hospitalization due to virologically confirmed COVID-19 disease g. VE in preventing death associated with virologically-confirmed COVID-19 clinical disease h. VE in preventing] all-cause LRTI (overall and stratified by hospitalization or not, irrespective of test result for SARS-COV-2. i. VE using Oxford Primary Outcome definition (PCR+ at least one symptom of fever > 37.8oC, cough, shortness of breath, anosmia, aguesia.) j. VE against N501Y.v2 variant of the SAR-CoV-2 virus
Secondary objective (Group 1 and Group 2)	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) b) Interferon-gamma (IFN-γ) enzyme- linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.

Exploratory immunology:	To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain	a.Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis. b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain "baits" to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity.

Table 4: Symptoms of Suspected COVID-19

Respiratory	**Non-Respiratory**
New onset cough	Fever or feverishness (defined subjectively, or objective fever ≥ 37.8°C, regardless of use of anti-pyretic medications)
New onset rapid breathing	Myalgia (or muscle ache)
New onset shortness of breath (or breathlessness or difficulty breathing)	Chills
Sore throat	Loss of taste (or taste disturbance)
Loss of smell (or smell disturbance)	Headache
Nasal congestion	Diarrhea
Runny nose	Tiredness (or fatigue or weakness)
	Nausea or vomiting
	Loss of appetite

Abbreviations: COVID-19 = coronavirus disease 2019.

Table 5: Efficacy Endpoint Definitions of COVID-19 Severity

COVID-19 Severity	Endpoint Definitions
Mild	Any one of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) • New onset cough • ≥ 2 COVID-19 respiratory/non-respiratory symptoms in Table 4 **AND** • Does not meet criteria for moderate or severe
Moderate	≥ 1 of: • Fever (≥ 37.8°C) + any 2 COVID-19 symptoms in table 4 for ≥ 3 days (need not be contiguous days) • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) • Any evidence of significant LRTI: – Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (beyond baseline) – Tachypnea: 20 to 29 breaths per minute at rest – SpO_2: < 94% on room air – Abnormal chest x-ray/CT consistent with pneumonia or LRTI – Adventitious sounds on lung auscultation
Severe	≥ 1 of: • Tachypnea: ≥ 30 breaths per minute at rest • SpO_2: < 92% on room air or PAO_2/FiO_2 < 300 • High flow oxygen therapy, CPAP, or NIV (eg, CPAP/BiPAP) • Mechanical ventilation or ECMO • One or more major organ system failure[a] (eg, cardiac/circulatory, pulmonary, renal, hepatic to be defined by diagnostic testing/clinical syndrome/interventions)

Abbreviations: BiPAP = bi-level positive airway pressure; CPAP = continuous positive air pressure; CT = computed tomography; ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; PAO_2 = partial pressure of oxygen in the alveolus; SpO_2 = oxygen saturation.

Evidence of major organ dysfunction or failure includes but is not limited to any of acute respiratory distress syndrome (ARDS), acute renal failure, acute hepatic failure, acute right or left heart failure, septic or cardiogenic shock, or requirement for vasopressors, systemic corticosteroids, or hemodialysis.

In adults living with HIV (HIV-infected)

Primary co-objectives:

- To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in adults living with HIV.
- To evaluate the immunogenicity of ChAdOx1 nCoV-19 after first and second doses of vaccine in adults living with HIV.

Table 6: Details of objectives Groups 3 (HIV-infected):

Objective	Objective details	Endpoint measures
Primary objective	To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 in people living with HIV	a) occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination; b) occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination; c) occurrence of unsolicited adverse events (AEs) for 28 days following vaccination; d) change from baseline for safety laboratory measures and; e) occurrence of serious adverse events; f) occurrence of disease enhancement episodes
Co-primary objective	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19 in people living with HIV after one and two doses of vaccine	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb) assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.
Secondary objective	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.	a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates) b) Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein c) Virus neutralising antibody (NAb)

		assays against live and/or pseudotyped SARS-CoV-2 virus d) Th1 and Th2 cytokine response profile at 3-4 days after vaccination.
Exploratory immunology:	To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain	a. Cellular Fc effector functionality assays to measure the ability of vaccine elicited antibodies to mediate cellular cytotoxicity, complement deposition, and phagocytosis. b. Flow cytometric sorting of plasmablasts and memory B cells to using spike and receptor binding domain "baits" to isolate SARS-CoV-2 specific B cells, sequence their immunoglobulin genes and define their epitope specificity.

5. TRIAL DESIGN

This is a Phase I/II, double-blinded, placebo-controlled, individually randomized study in adults aged 18-65 years living with and without HIV in South Africa. ChAdOx1 nCoV-19 or placebo will be administered via an intramuscular injection into the deltoid. The protocol has been adapted to confirm that the study will assess safety, immunogenicity and efficacy of two doses of ChAdOx1 nCoV-19 based on the phase I study results from the UK immunogenicity cohort.[16] For Group-1 (HIV-uninfected adults; n=70) and Group-3 (HIV-infected adults; n=100), a two dose schedule spaced 21-35 days apart will be evaluated for safety and immunogenicity. In Group II (phase II; immunogenicity and efficacy cohort), we will target enrolling 1900 participants to accrue sufficient number of endpoints to analyze for efficacy of at least 60% (and a lower bound of >0%) and 80% power assuming an attack rate of 3.5% for COVID-19 in the placebo arm (see sample size section). Based on the endpoint case accrual and the trajectory of the epidemic in South Africa, the sample size may be adjusted in relation to number of endpoints being accrued. Participants already enrolled prior to implementation of Version 3.0 of the protocol, that tested positive for SARS-CoV-2 by PCR at randomization will continue on the study, including all further scheduled visits and procedures. However, an equal number of additional participants that test negative for SARS-CoV-2 on PCR testing will be enrolled into the study.

The three trial groups are detailed in Table 7, with an overall sample size of ~2070. Randomisation will take place at an intervention to placebo ratio of 1:1 in blocks of 8 and all participants and clinical study staff will be blinded to IP or placebo. Site pharmacists and the person administering the allocated IP/placebo will be unblinded. Once group 1 is fully recruited, safety data will be reviewed by DSMC. Group 3 enrolment will follow on from group 1 enrolment. This decision will be guided by DSMC review of COV001 trial in the UK. Initiation of enrolment into Group 2 will be contingent upon review by the joint DSMC of the ongoing study in the UK, which will also ultimately inform whether to pursue a single or two-dose schedule for the efficacy-cohort in South Africa.

Participants will be followed over the duration of the study (through to 365 days post-randomization) to record adverse events and episodes of virologically confirmed symptomatic COVID-19. Participants will be tested for SARS-CoV-2 infection if they present with a new onset of symptoms suggestive of COVID-19 (Table 4) throughout the duration of their participation.

Detailed clinical parameters will be collected from medical records (or examination by study-staff) and aligned with the COVID-19 score; Table 5. These include measuring severity based on oxygen saturation, need for oxygen therapy, respiratory rate and other vital signs, need for ventilatory support, X-ray imaging and blood test results, amongst other clinically relevant parameters; Table 5.

Safety will be assessed in real time and at least monthly interim reviews by the DSMC will be scheduled after Group 1 (70 HIV-uninfected) participants received the IP (dose 1 and dose 2 if given), after enrolment of 100 HIV-infected adults (Group-3) and once all Group-2 participants are enrolled. The DSMC will periodically assess safety and efficacy data every 4-8 weeks and/or its discretion. All deaths and any serious adverse event considered to be study-related will be reviewed by the DSMC within 72 hours of site reporting of such cases to the DSMC (which will occur within 24 hours of site identification on any such cases).

Table 7: Trial groups

Group #	Group description	Objective	Follow up	Treatment	Vaccination schedule
1 (n=70)	People without HIV (HIV-uninfected)	Intensive Safety and immunogenicity	Intensive	ChAdOx1 nCoV-19 5-7.5x1010 vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
2a (n=250)§	People without HIV (HIV-uninfected)	Safety, intensive immunogenicity and vaccine efficacy	Extended	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
2b (n=1650) §	People without HIV (HIV-uninfected)	Safety, immunogenicity and vaccine efficacy	Extended	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	2* doses, 4 weeks (21-35 days) apart
3 (n=100)	People living with HIV (HIV-infected),	Intensive Safety and immunogenicity	Intensive	ChAdOx1 nCoV-19 5-7.5x10^{10} vp; OR Normal saline (0.9% NaCl)	Prime-boost 2* doses, 4 weeks (21-35 days) apart

¥Sample size increased from 50 to 70, following higher than anticipated positivity for SARS-CoV-2 infection (six of initial 24 randomized into the study), to accommodate for non-evaluable (i.e. not COVID-19 naive) participants.

*Participants will receive 2 doses of the same injection (EITHER IP or placebo) as assigned at randomization.

§Numbers will be increased to supplement for corresponding number of individuals randomized prior to implementation of Version 3.0 of the protocol that tested positive for SARS-CoV-2 on PCR at time of randomization.

Following a review of the initial safety/immunogenicity trial being conducted in the UK; COV0001 trial, and review of the initial safety/ immunogenicity trial COV0001 by the DSMC, it was decided that Group 2 in this trial will receive 2 doses of assigned study intervention. SAHPRA and WHREC have already been informed of Group 2 receiving a two-dose schedule based on the earlier version of the protocol.

Also, 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. This will involve enrolling up to a total of 1900 people in Group-2, which will provide 80% power to detect at least a 60% vaccine efficacy (lower bound of 95%CI >0) with an attack rate of 3.5% in the placebo arm. Ongoing review of the number of COVID-19 endpoint cases accrued during the course of the study, may lend itself to enrolling smaller number of participants should the attack rate be higher than 3.5%. The sample size for Group 1 has been increased to 70 to accommodate for the higher than anticipated infection rate with SARS-

CoV-2 (6 of the initial 24 participants randomized in group 1). Similarly, in anticipation of approximately one-third of Group-3 participants possibly being already infected with SARS-CoV-2, the sample size will be increased to 100 to have approximately 30 sero-negative vaccinees and placebo recipients enrolled into the study.

5.1. Trial participants

Adult participants (healthy HIV-uninfected; and generally well people living with HIV [Group 3]) aged 18-65 years will be enrolled. Participants will be considered enrolled immediately following randomization to receive first vaccination.

5.2. Definition of End of Trial

The end of the trial is the date of the last assay conducted on the last sample collected.

5.3. Duration of study

The total duration of the study will be 12 months from the day of enrolment for all participants.

5.4. Potential Risks for participants

The potential risks are those associated with phlebotomy, vaccination and disease enhancement

5.4.1. Venipuncture

Localised bruising and discomfort can occur at the site of venipuncture. Infrequently fainting may occur. These will not be documented as AEs if they occur. The total volume of blood drawn over a six-month period will be 160- 315mL (blood volumes may vary slightly for participants at different investigator sites due to use of different volume vacutainers, following local SOPs). This should not compromise these participants, as they would donate 470mL during a single blood donation for the National Blood transfusion Service over a 3-4-month period. Participants will be asked to refrain from blood donation for the duration of their involvement in the trial.

5.4.2. Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (about 1 in 1,000,000 vaccine doses) but can occur in response to any vaccine or medication.

5.4.3. Vaccination

Local reaction from IM vaccination

The typical local reaction as a result of IM injection is temporary pain, tenderness, redness, and swelling at the site of the injection.

Systemic reactions

Constitutional influenza-like symptoms such as fatigue, headache, malaise, feverishness, and muscle aches can occur with any vaccination and last for 2-3 days. Presyncopal and syncopal episodes may occur at the time of vaccination which rapidly resolve. As with any other vaccine, temporary ascending paralysis (Guillain-Barré syndrome, GBS) or immune mediated reactions that can lead to organ damage may occur, but this should be extremely rare (1 in 100,000-1,000,000 vaccine doses).

Control participants will receive a placebo injection containing sterile normal saline (0.9% NaCl). The volume of the IP and placebo injections will be equal.

5.4.4. Disease Enhancement

The risks of inducing disease enhancement and lung immunopathology in the event of COVID-19 disease following ChAdOx1 nCoV-19 vaccination are unknown. Challenge studies on ferrets and Non-human primates (NHPs) are underway and results will be reviewed as they emerge. All pre-clinical data from challenge studies using ChAdOx1 nCoV-19 and other vaccine candidates (when available) will inform decisions on risks and benefits to participants receiving the IP.

5.5. Known Potential Benefits

Recipients of ChAdOx1 nCoV-19 do not have any guaranteed benefit. However, the information gained from this study could contribute to the development of a safe and effective vaccine against COVID-19. IP recipients may benefit from receipt of the ChAdOx1 nCoV-19 vaccine if the vaccine is found to be effective against reducing COVID-19. Placebo recipients will not benefit from receipt of placebo, however, may benefit from regular follow-up during the SARS-CoV-2 pandemic as they will be tested for infection if they are symptomatic.

6. RECRUITMENT AND WITHDRAWAL OF TRIAL PARTICIPANTS

6.1. Identification of Trial Participants

Adults in South Africa will be recruited by the following methods:

- Research sites will utilize databases available in the research units which contain contact details of participants or parents of participants in previous (completed) vaccine trials.
- Adverts, approved by local ethics committee, may be utilized and places in health care clinics and other public places.
- Radio announcements
- Community engagement via the community action boards affiliated to the research sites

6.2. Informed consent

All participants will have the opportunity to read the information sheet prior to or during screening visit. An 'assessment of understanding' (AOU) will be completed by participant to assess their understanding of participant information sheet. Participants will have the opportunity to discuss the trial information with investigators and family members. Informed consent will be signed and dated before any study specific procedures are performed. The informed consent process will be undertaken in two stages. In the first instance, following brief introduction about the study at the screening visit, including inclusion and exclusion criteria, volunteers will be asked to consent to procedures to determine their eligibility for possible randomization (full-study participation). This will include collection of key demographic information, a brief clinical history, testing inter alia for HIV-1 infection (except for Group 3), Hepatitis B surface antigen (HBsAG) positivity, evidence for current (by molecular detection) infection with SARS-CoV-2, pregnancy test (for women of reproductive age group), HbA1C (glycosylated hemoglobin) as well as general physical well-being (including blood pressure check). This approach has been adopted to accommodate for the higher than anticipated number of participants (six of 24) that tested positive for SARS-CoV-2 infection by PCR after having started enrolment of Group-1 participants.

Following fulfilment of inclusion and exclusion criteria based on findings from the screening visit, those who remain eligible and agree to undergo randomization into the full study, will be consented further for study participation. Screened participants will be encouraged to take complete informed (enrolment) consent forms home from the screening visit, and read and discuss the trial and their possible involvement in the trial with family. At the randomization visit, the participant will be fully informed of all aspects of the trial, the potential risks and their obligations. The following general principles will be emphasized:

Participation in the study is entirely voluntary

Refusal to participate involves no penalty or loss of medical benefits

The participant may withdraw from the study at any time.

The participant is free to ask questions at any time to allow him or her to understand the purpose of the study and the procedures involved

The study involves research of an investigational vaccine

There is no direct benefit to the participant from participating

Participants will be asked to provide detailed medical and surgical history to investigator

verbally and if possibly, patient-held medical records (outpatient cards) will be reviewed.

Blood samples taken as part of the study may be sent to laboratories outside South Africa (e.g. University of Oxford and InNexus BioPharma Inc in Canada) for immunogenicity testing. These will be anonymised samples. Participants who agree to full study participation will be asked if they consent to storage of any leftover samples for use in other ethically approved research for up to 25-year period, which will be optional.

The aims of the study and all tests to be carried out will be explained. The participant will be given the opportunity to ask about details of the trial, and will then have time to consider whether or not to participate. If they do decide to participate, the participant and the investigator will sign and date the relevant screening consent form, and full-study participation consent form (if eligible). However, in the current crisis, there may be occasions when it is necessary for the consent form to be signed by an appropriately trained and delegated research nurse instead of the investigator. The participant would always have the opportunity to discuss the study with a medically qualified investigator if they wish. The participant will then be provided with a copy of the consent forms to take away and keep, with the original being stored in the case report form (CRF).

6.3. Inclusion and exclusion criteria

This trial will be conducted in generally healthy adults without HIV, except for Group-3 (i.e. safety and immunogenicity in people with HIV).

6.3.1. Inclusion Criteria for all participants

The participants must satisfy all the following criteria to be eligible for the trial:

- Healthy adults aged 18-65 years.
- Documented result of not being infected with HIV (including screening by a rapid HIV antibody test) within two weeks of randomization into the study for Group-1 and Group-2 participants only.
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow investigators review available medical records, and review all medical and laboratory records if participant is admitted to hospital with respiratory tract infection suspected or confirmed to be COVID-19.
- For females only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening (within 14 days of randomization) or vaccination.
- For Group-3 only (i.e. HIV-infected), need to have been on anti-retroviral treatment for at least three months and HIV-1 viral load is <1,000 copies/ml within two weeks of randomization.

- Agreement to refrain from blood donation during the course of the study.
- Provide written informed consent.

6.3.2. Exclusion Criteria

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

- Planned receipt of any vaccine other (licensed or investigational) than the study intervention within 30 days before and after each study vaccination.
- Use of any unproven registered and unregistered treatments for COVID-19.
- Evidence of current SARS-CoV-2 infection detected by molecular assay detection of SARS-CoV-2 done within 96 hours prior to randomization.
- Acute respiratory and/or non-respiratory illness consistent with potential COVID-19 (see Table 4 for list of symptoms) concurrent or within 14 days prior to first study vaccination (medical history and/or physical examination) or documented temperature of > 38°C during this period. NOTE: This is a temporary exclusion for which the subject may be re-evaluated if they remain free from acute respiratory and/or non-respiratory illness consistent with potential COVID-19 after 14 days. Should a subject have a SARS-CoV-2 positive test, they may NOT be randomized.
- Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines).
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
- HbSAg positivity on the screening sample, or any sample obtained within three months of randomization.
- Grade 2 or higher level of abnormality for FBC, U&E or LFT based on DAIDS Grading Criteria (Version 2.1, July 2017)
- History of allergic disease or reactions likely to be exacerbated by any component of the ChAdOx1 nCoV-19 vaccine.
- Any history of hereditary angioedema or idiopathic angioedema.
- Any history of anaphylaxis in relation to vaccination.
- Pregnancy, lactation or willingness/intention to become pregnant during the study.
- History of cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition likely to affect participation in the study.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of

significant bleeding or bruising following IM injections or venipuncture.

- Any other serious chronic illness requiring hospital specialist supervision.
- Chronic respiratory diseases, including poorly controlled/ unstable asthma
- Chronic disease inclusive of:

  a) hypertension if ≥Grade 2 based on DAIDS AE Grading Version 2.1-July 2017

  b) congestive heart failure;

  c) chronic obstructive pulmonary disease by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of ≥ 2;

  d) evidence of coronary artery disease as manifested by cardiac interventions or cardiac medications for control of symptoms;

  e) chronic type 2 diabetes (adult onset) requiring insulin;

  f) chronic kidney disease/renal insufficiency;

  g) chronic gastrointestinal and hepatic diseases; or

  h) chronic neurological diseases.

- Seriously overweight (BMI ≥ 40 Kg/m^2)
- Suspected or known current alcohol abuse as defined by an alcohol intake of greater than 42 units every week (% alcohol x volume (ml)/1000= number of units; e.g. Normal beer= 2 units, Glass of wine =3 units).
- Suspected or known injecting drug abuse in the 5 years preceding enrolment.
- Any clinically significant abnormal finding on screening urinalysis.
- Any other significant disease, disorder or finding which may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study or impair interpretation of the study data.
- History of laboratory confirmed COVID-19 illness or known close contact with a person that was infected with SARS-COV-2. Close contact refers to being in contact with someone in the same household, or for at least 15 minutes and in close proximity with an infected person in the absence of wearing of a face masks.
- New onset of fever or a cough or shortness of breath in the 30 days preceding screening and/or enrolment

- In addition to above, Group 1 & 2 participants need to fulfil the following exclusion criteria: Any confirmed or suspected immunosuppressive or immunodeficient state, including HIV infection; asplenia; recurrent severe infections and chronic use (more than 14 days) immunosuppressant medication within the past 6 months (topical steroids are allowed).

- Any confirmed or suspected immunosuppressive or immunodeficient state (except HIV infection for Group-3), asplenia, recurrent severe infections and chronic use (more than 14 days) immunosuppressant medication within the past 6 months (topical steroids are allowed).

Note: Stable endocrine disorders that have a confirmed autoimmune etiology (eg, thyroid, pancreatic), including stable diabetes not requiring insulin are allowed.

Should participants develop COVID-19 prior to the second dose of vaccine, or test positive for SARS-CoV-2 infection and be asymptomatic, the participants will remain eligible to receive a second dose of assigned study-intervention. The second dose of assigned study-drug will however be delayed for at least: i. 14 days in individuals that had asymptomatic SARS-CoV-2 infection, ii. 14 days after symptom resolution if mild illness; iii. 28 days after illness onset following moderate or severe illness, and is clinically stable based on the discretion of the investigator; iv. For cases requiring hospitalization for COVID-19, the 2nd dose should be delayed for at least 14 days post-discharge and participant needs to be clinically stable.

6.3.3. Re-vaccination exclusion criteria

The following AEs associated with any vaccine, or identified on or before the day of vaccination constitute absolute contraindications to further administration of an IP to the participant in question. If any of these events occur during the study, the participant will continue follow-up in the study but will not receive any further study investigational vaccine:

- Anaphylactic reaction following administration of vaccine
- Pregnancy

6.3.4. Effective contraception for female participants

Female participants of childbearing potential (any woman or adolescent who has begun menstruation) are required to use an effective form of contraception during the course of the study (i.e. until their last

follow-up visit).

Acceptable forms of contraception for female participants include:

Established use of oral, injected or implanted hormonal methods of contraception.

Placement of an intrauterine device (IUD) or intrauterine system (IUS).

Total abdominal hysterectomy.

Bilateral tubal Occlusion

Barrier methods of contraception (condom or occlusive cap with spermicide).

Post-menopausal women, defined as a woman over the age of 45 who has not had a menstrual period for at least 12 months.

Female participants will be requested to continue obtaining their contraceptives from their nearest clinic, which is provided at no-cost in the public-sector. Should this not be feasible, the study will provide female participants with the contraceptives.

Female participants in a same-sex relationship and women that are post-menopausal will not be required to be on contraception.

6.3.5. Prevention of 'Over Participating'

Participants will be excluded from the study if they are concurrently involved in another trial where an IP has been administered within 30 days prior to enrolment, or will be administered during the trial period. They will not be enrolled they are actively registered on another investigational vaccine or medication trial.

6.3.6. Withdrawal of Participants

In accordance with the principles of the current revision of the Declaration of Helsinki and any other applicable regulations, a participant has the right to withdraw from the study at any time and for any reason, and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the interests of the participant's health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

Administrative decision by the Investigator.

Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).

Significant protocol deviation.

Participant non-compliance with study requirements.

An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilized or a non-trial related causality has been assigned. The DSMC or DSMC chair may recommend withdrawal of participants.

Any participant who is withdrawn from the study may be replaced, if that is possible within the specified time frame.

If a participant withdraws from the study, data and blood samples collected before their withdrawal will still be used on the analysis. Storage of blood samples will continue unless the participant specifically requests otherwise.

In all cases of participant withdrawal, long-term safety data collection, including some procedures such as safety bloods, will continue as appropriate if participants have received one or more vaccine doses, unless they decline any further follow-up.

6.4. Pregnancy

Should a participant become pregnant during the trial, no further study IP will be administered. She will be followed up for clinical safety assessment with her ongoing consent and in addition will be followed until pregnancy outcome is determined. We would not routinely perform venipuncture in a pregnant participant unless there is clinical need. Women falling pregnant during the study will also continue in follow-up for COVID-19 and be retained in the efficacy analyses. A 'Pregnancy reporting' form must be completed within 7 days of site staff becoming aware of the pregnancy, and a pregnancy outcome form must be completed within 7 days of delivery, or as soon as possible (within 7 days of site awareness) if site is notified more than 7 days post-delivery.

7. TRIAL PROCEDURES

This section describes the trial procedures for evaluating study participants and follow-up after administration of study vaccine.

7.1. Schedule of Attendance

All participants in groups 1 and 3 will have the same schedule of clinic attendances and procedures as indicated in the schedules of attendance (Table 8). Participants will receive either the ChAdOx1 nCoV-19

vaccine or NaCl (0.9%) placebo injection, and undergo follow-up for a total of 12 months' post enrolment. The total volume of blood donated during the study will be 160-315mL depending on which group they are allocated to. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, urine microscopy in the event of positive urinalysis or additional blood tests if clinically relevant.

7.2. Observations

Pulse, respiratory rate, oxygen saturation, blood pressure and temperature will be measured at the time-points indicated in the schedule of procedures and may also be measured as part of a physical examination if indicated at other time-points.

7.3. Blood tests, Nasal swab/saliva and urinalysis

Blood will be drawn for the following laboratory tests and processed at an accredited Laboratory for:

Haematology; Full Blood Count and differential count (Groups 1 and 3)

Biochemistry; U&E (Sodium, Potassium, Urea, Creatinine), Liver Function Tests (Albumin, ALT, ALP, Bilirubin) (Groups 1 and 3)

Diagnostic serology; HBsAg, HIV antibodies (specific consent will be gained prior to testing blood for these blood-borne viruses). HIV Elisa will be repeated on HIV-negative participants at trial conclusion visit (day 364). HbA1C will be done on all participants, and those with an abnormal result will be referred for further medical care, but remain eligible for study enrolment. (All Groups)

Genetics; Human Leukocyte Antigen (HLA) typing (All Groups)

COVID-19 PCR processing (nasal swab and/or saliva)

A nasal swab and/or saliva will be collected for testing of SARS-COV-2. Sample processing will be done at the RMPRU using molecular detection methods, with confirmatory testing at another accredited laboratory. In the case of discordant results between RMPRU and the second laboratory, a further aliquot of the sample will be submitted to a third accredited laboratory for testing, and the result from the third laboratory will be assumed to be the final result.

Additional safety blood tests may be performed if clinically relevant at the discretion of the medically qualified investigators, including potential prognostic indicators or markers of severe COVID-19 disease.

Urinalysis; Urine will be tested for protein, blood and glucose at screening. For female participants only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at screening and immediately prior to vaccination.

Immunology; Immunogenicity will be assessed by a variety of immunological assays.

Serum IgG and IgM: The serum samples will be analysed by ELISA or on other appropriate immuno-assays platforms such as Luminex) for titres of IgG and IgM to two different versions of the spike protein (full length spike protein and receptor binding domain (RBD). These proteins are the major targets for neutralizing antibodies for SARS-CoV-2. Plasmids for these proteins were procured from the laboratory of Prof Florian Krammer, Mount Sinai USA and proteins were successfully expressed and purified in the laboratory of Prof Penny Moore at NICD, South Africa. Fluorescence based micro-bead immunosorbent assay for IgG against SARS-CoV-2 whole length spike protein and the RBD domain on luminex platform has been developed at RMPRU and assay harmonization will be done in collaboration with Prof. Andrew Pollard lab, Oxford University, United Kingdom.

This will be a two-step analysis in which first step includes screening of serum samples against the RBD and second step in which positive samples from the first step undergo a confirmatory testing against the full length spike protein. COVID-19 IgG assay against RBD and Spike protein has been set up at RMPRU and checked for sensitivity (compared to PCR positivity) and specificity (using serum samples from pre COVID months, Sep, Oct, Nov, Dec 2019). Covid 19 IgM assay set up underway. In house reference serum for both IgG and IgM will be developed by pooling convalescent serum from COVID-19 positive participants, and will be calibrated against standard reference reagent from National Institute for Biological Standards and Control (NIBSC), which is providing references sera to laboratories as part of a WHO COVID-19 serology working groups. COVID-19 assay will be further harmonized using NIBSC serum panel which includes high, medium and negative control serum panel. Each luminex run will include in-house high, medium and negative serums for quality control. The assay will further expand to IgA for breast milk analysis.

In addition, samples may be sent to the Oxford collaborators group, and possibly another reference group for further testing.

Ex vIvo- Elispot Assay:

The *ex vivo* IFN-gamma ELISpot assay, will be used to quantify the frequency of antigen-specific effector T cells in response to vaccination. The assay will be performed on standardized procedure from Oxford University. Pools of peptides needed for the assay will be supplied from Oxford University. For Elispot assay, peptides are designed to cover the length of the SARS-CoV2 spike construct and comprise 15mer peptides overlapping by 10 aa, giving a total of 258 peptides.

Cytokine analysis: Serum samples will be analysed at RMPRU for a panel of 25 cytokines which includes

TH1 cytokines (IFN-γ and interleukin (IL)-2), TH2 Cytokines (IL-4, IL-5, IL-6, IL-10, and IL-13) and other pro-inflammatory markers such as TNF-α on multiplex bead-based immunoassay using commercial kits as per manufacturer instructions (Novex, Human Cytokine Magnetic 25-Plex PanelCatalog #: LHC0009M).

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.

Pseudotyped neutralization assay:

The SARS-CoV-2 neutralization assay (optimized in collaboration with Dr Nicole-Doria-Rose, VRC) is an adaptation of a highly validated HIV neutralization assay routinely in use at the NICD. The SARS-CoV-2 assay measures neutralization of pseudotyped virus in ACE2-over-expressing 293T target cells (developed by Dr Michael Farzan, The Scripps Research Institute) as a function of a reduction in Luc reporter gene expression. The pseudotyped virus consists of lentiviral particles that are deficient for lentiviral env, but have surface SARS-CoV-2 spike protein and package the gene for firefly luciferase. Infected cells express luciferase, and luciferase activity is quantified by relative light units (RLU) of luminescence. Virus is applied to cells with or without pre-incubation with antibodies; neutralizing antibodies reduce infection, resulting in lower RLUs. Serial dilution of antibodies can be used to produce a dose-response curve to quantify potency. The assay is performed in 96-well flat-bottom black culture plates for high throughput capacity and enhanced luciferase signal Use of a clonal cell line provides enhanced precision and uniformity. Controls will be neutralizing monoclonal antibodies expressed in-house as well as COVID-19 HIV positive and negative serum samples.

Live virus neutralization assays:

This assay, being developed at the NICD by Prof Janusz Paweska utilizes live SARS-CoV-2 coronavirus cultured for one week in Vero cells. After visualization of microscopic cytopathic effects by microscopy, cultures are confirmed positive by PCR and viral stocks cryopreserved. Microneutralization assays will be performed by incubation of SARS-CoV-2 virus with Vero cells with or without pre-incubation with antibodies. Neutralizing antibodies reduce infection, resulting in reduced cytopathic effect. Cross-validation of the live and pseudotyped neutralization assays will be performed using shared SARS-CoV-2 convalescent sera and neutralizing monoclonal antibodies expressed in-house.

Fc effector functionality, including antibody dependent cellular cytotoxicity, complement deposition, and phagocytosis will assess responses to spike trimer or the receptor binding domain. ADCC will use spike trimer or receptor binding domain (RBD)-coated Huh7 cells that express the SARS-CoV-2 receptor ACE-2. Targets for ADCD and ADCP will be neutravidin fluorescent beads coated with spike or RBD proteins.

Targets will be incubated with SARS-CoV-2 convalescent sera. Effector cells for ADCC will be PBMCS from uninfected donors, and will measure granzyme B. ADCD will be measured as the amount of C3b deposition on the surface of antigen-coated beads. ADCP will be measured as the percentage of antigen-coated beads taken up by THP-1 cells in an antibody dependent manner. In addition, samples may be sent to the Oxford collaborators group, and possibly another reference group for further testing. A detailed update of the specific immunology assays to be used in this study will be provided prior to enrolling the first subject in the study.

Other exploratory immunological assays including antibody subtype assays, DNA analysis of genetic polymorphisms potentially relevant to vaccine immunogenicity, monoclonal antibody isolation and gene expression studies amongst others may be performed at the discretion of the Investigators.

Collaboration with other specialist laboratories in South Africa, the UK, Europe, Canada and elsewhere for further exploratory tests may occur. This would involve the transfer of serum or plasma and, PBMC and/or other study samples to these laboratories, but these would remain anonymised. Informed consent for this will be gained from participants. Samples collected for the purposes of COVID-19 diagnosis will be sent to reference laboratories in South Africa for confirmatory testing.

All participants testing positive for SARS-COV2 will be notified through the Notifiable Medical Conditions, per regulatory requirements in South Africa, and includes providing personal data to implement isolation measures of infected individuals and tracing of their contacts. Participants will be informed the obligation on the part of the investigators to submit this level of information to the Notifiable Medical Conditions registry, and local authorities that are responsible for monitoring of infected cases and their contacts.

Participants will be informed that there may be leftover samples of their blood (after testing for this study is completed), and that such samples may be stored up to 25 years for possible future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity. Participants will be able to decide if they will permit such future use of any leftover samples. With the participants' informed consent, any leftover cells, urine and serum/plasma will be frozen for future analysis of COVID-19 and other coronaviruses related diseases or vaccine-related responses. If a participant elect not to permit this, all of that participant's leftover samples will be discarded after the required period of storage to meet Good Clinical Practice (GCP) and regulatory requirements.

Samples that are to be stored for future research will be stored at RMPRU.

7.4. Study visits

The study visits and procedures will be undertaken by one of the clinical trials team. The procedures to be included in each visit are documented in the schedule of attendances. Each visit is assigned a time-point and a window period, within which the visit will be conducted.

7.4.1. Screening visit

Participants will be required to share past medical and past surgical history, and medication at screening visit as an initial confirmation of eligibility. All potential participants will have a screening visit, which may take place up to 14 days prior to vaccination, although some results such as molecular testing for SARS-CoV-2 need to be done within 96 hours of randomization. The screening informed consent will be taken before screening. If consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including a medical history, physical examination, blood tests and height and weight. Individually each participant will have the opportunity to question an appropriately trained and delegated researcher before signing the full-study participation consent at enrollment visit.

Abnormal clinical findings from the urinalysis or blood tests at screening will be assessed by a medically qualified study member. Abnormal clinical and blood tests following screening will be assessed according to specific laboratory adverse event grading tables (DAIDS Laboratory Grading of Abnormal Results; Version 2.1, July 2017). Any abnormal test result deemed clinically significant may be repeated to ensure it is not a single occurrence. If an abnormal finding is deemed to be clinically significant (Grade 2 or higher abnormality), the participant will be informed and appropriate medical care arranged with the permission of the participant.

The eligibility of the participant will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the participant from enrolling in the trial or to withdraw a participant from the trial will be based on fulfilling the inclusion and exclusion criteria, as well as at the discretion of the Investigator. If eligible, a day 0 visit will be scheduled for the participant to receive the vaccine and subsequent follow-up. Participants will be consented for full study participation prior to randomization at the day-0 visit.

If more than 14 days elapse between screening and an eligible and willing participant presents for enrolment, re-screening will be required. Informed consent should be verified and discussion recorded in source document. All applicable screening procedures, except for HIV if negative in the past three months should be repeated at re-screening visit. Also, if applicable, safety bloods should be repeated, to ensure that they are done ≤14 days prior to vaccination, and SARS-CoV-2 swab needs to be done in

96 hours prior to randomisation.

7.4.2. Day 0: Enrolment and vaccination visit

Participants will be considered enrolled into the trial at the point of written, signed consent for full-study participation, i.e. following confirmation of eligibly through the screening visit. The initiation of the consenting process for full-study participation may precede the date on which the consent form is signed, to allow adequate time for potential participants to consider their willingness to participate. Before randomization, the eligibility of the participant will be reviewed. Pulse, respiratory rate, oxygen saturation, blood pressure and temperature will be observed and if necessary, a medical history and physical examination may be undertaken. Vaccinations will be administered as described below.

7.4.3. Vaccination

All vaccines will be administered intramuscularly according to specific SOPs. The injection site will be covered with a sterile dressing and the participant will stay in the trial site for observation, in case of immediate adverse events. Observations will be taken 60 minutes after vaccination (+/- 30 minutes). Post-vaccination observations include pulse rate, respiratory rate, oxygen saturation, blood pressure, temperature and vaccination site review.

In all groups, participants will be given an oral thermometer, measurement device and diary card (paper or electronic), with instructions on use, along with the emergency 24-hour telephone number to contact the on-call study doctor if needed. Participants will be instructed on how to self-assess the severity of these AEs. There will also be space on the diary card to self-document unsolicited AEs, and whether medication was taken to relieve the symptoms. Diary cards will collect information on the timing and severity of the following solicited AEs:

Table 8: Solicited AEs as collected on post vaccination diary cards

Local solicited AEs	Systemic solicited AEs
Pain	Fever
Tenderness	Feverishness
Redness	Chills
Warmth	Joint pains
Itch	Muscle pains
Swelling	Fatigue
Induration	Headache
	Malaise
	Nausea

7.4.3.1. Sequence of Enrolment and Vaccination of Participants

Prior to initiation of the study, any newly available safety data will be reviewed from animal studies (including non-human primate studies being conducted in UK) and clinical trials of coronavirus vaccines (including data from first 50 participants being enrolled in similar trial in UK, COV001) being tested elsewhere, and discussed with the DSMC and/or regulatory and ethics committees as necessary. Participants in group 1 (HIV-uninfected adults, prime-boost 2-dose, intensive follow up) and Group-3 may be enrolled concurrently, contingent upon approval by the DSMC.

Based on the immunogenicity data from the initial safety/immunogenicity cohort enrolled in the UK study (COV001) and following review by the DSMC it was decided that all participants will receive two doses of the assigned study-intervention. A notification on the dosing schedule for Group-2 was submitted the Ethics committee and SAPHRA.

7.4.4. Subsequent visits:

Follow-up visits will take place as per the schedule of attendances described in Table 8, Table 9 and Table 10 with their respective windows. Participants will be assessed for local and systemic adverse events, interim history, physical examination, review of diary cards (paper or electronic) and blood tests at these time points as detailed in the schedule of attendances. Blood will also be taken for immunology purposes.

If participants experience adverse events (laboratory or clinical), which the investigator (physician), CI and/or DSMC chair determine necessary for further close observation, the participant may be admitted to a hospital for observation and further medical management under the care of the attending-physicians.

7.4.5. Participants under quarantine

Given the evolving epidemiological situation both globally and in South Africa, should a participant be under isolation or quarantine and unable to attend any of the scheduled visits, a telephone consultation will be arranged in order to obtain core study data where possible. Any study samples from participants under quarantine or isolation will be collected at the place of residence at the time of the participant (or in hospital if hospitalized), by trained study staff with appropriate precautionary measures being implemented (including use of protective personal equipment).

7.4.6. Telephonic follow up contact

Participants will be contacted telephonically at least fortnightly during periods when circulation of SARS-CoV-2 is high in the region covered by the sites. Trial staff will ask participants if they have had any symptoms of COVID-19 or close contact with a known COVID-19 case in the past week. Participants who have had any symptoms or close contact with a known COVID-19 case will be asked to attend trial site clinic for a nasal swab for SARS-CoV-2.

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Table 8: Schedule of visits: Groups 1 & 3

Visit number	Screening	V1	V2	V3	V4	V5	V6*	V7*	V8*	V9*	V10	V11	COVID-19
Day #	-14 to -1	0 (Vax1)	3	7	14	28 (Vax2)	31	35	42	56	182	364	Illness
	Screening	D0	V1+ 3 days ±1; (day 2-4)	V1 +7 days ±2 (day 5-9)	V1+ 14 days ±3 (day 11-17)	Visit 1 + 28 days ±7 day 21-35)	V5+3 days ±1	V5+7 days ±2	V5+14 days ±3	V5 +28 (±7)	D182 (±14)	D364 (±14 days)	As required [$]
Eligibility	X	X											
Consenting	X[§]	X[¥]											
Inclusion/ exclusion	X	X				X							
Contraindications	X	X				X							
Vital signs [#]	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X												X
Physical examination	X (full)	X	X	X	X	X (full)	X	X	X	X	X	X	X (full)
Vaccination		X				X							
Post vaccination obs		X	X (deltoid)	X (deltoid)		X	X (deltoid)	X (deltoid)					
Diary cards provided		X				X							X (illness DC)
DC collected				X				X					
Safety bloods (FBC, U&E, LFT)	X		X	X		X		X		X			
Screening bloods (HBsAg, , HIV, HbA1C)	X											X (HIV Gr 1)	
HIV Viral load and CD4 (Grp 3 only)	VL and CD4												
Immunology bloods***		E, PAX (12.5-17.5ml)	Cyt, PAX (12.5 - 17.5ml)		E & CMI (20-25ml)	E, N, PAX (17.5-22.5ml)		Cyt (10-15mls)	E & N & CMI (25-30ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X												

Urinalysis bHCG (women only)	X	(X)				X							
Nasal swab/ saliva	X (V1-96 hours)	X		X	X	X		X	X	X	X	X	X

* Visit 5 to Visit 9 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.

§ Screening informed consent form (ICF).

¥Full study participation informed consent form, if remain eligible after completion of screening procedures.

Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E =Elisa; Cyt= Th1 and Th2 cytokine profile; N= neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay, PAX= PAXgenes.

Blood test summary:

- Screening: Safety bloods (Full Blood Count, FBC; Urea and Electrolytes, U&E; Liver Function tests, LFT); Screening bloods (HBsAg, HIV, Glycosylated hemoglobin; HbA1c), In group 3 only- CD4+ -lymphocyte count, CD4+ & VHIV-1 viral load, VL)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Safety bloods (FBC, U&E, LFT)
- Visit 4 Immunogenicity- Elisa & cell-mediated immunity
- Visit 5 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Visit 6 NIL
- Visit 7 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 8 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity
- Visit 9 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa
- Visit 10 Immunogenicity- Elisa
- Visit 11 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assays
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

Table 9: Visit schedule for group 2a

Visit number	Screening	V1	V2	V3	V4	V5*	V6*	V7*	V8	V9	COVID-19
Day #	-14 to -1	0 (Vax1)	7	14	28 (Vax2)	35	42	56	182	364	Illness
	Screening	D0	V1 +7 days ±2 (day 5-9)	V1+ 14 days ±3 (day 11-17)	Visit 1 + 28 days ±7	V4+7 days ±2	V4+14 days ±3	V4 +28 (±7)	D182 (±14)	D364 (±14 days)	As required [$]
Eligibility	X	X									
Consenting	X[§]	X[¥]									
Inclusion/ exclusion	X	X			X						
Contraindications	X	X			X						
Vital signs [#]	X	X	X	X	X	X	X	X	X	X	X
Medical history	X										X
Physical examination	X (full)	X	X	X	X (full)	X	X	X	X	X	X (full)
Vaccination		X			X						
Post vaccination obs		X	X (deltoid)		X	X (deltoid)					
Diary cards provided		X			X						X (illness DC)
DC collected			X			X					
Screening bloods (HBsAg, , HIV, HBA1C)	X									X (HIV)	
Immunology bloods***		E, PAX (12.5-17.5ml)	Cyt, PAX (12.5 -17.5ml)	E & CMI (20-25ml)	E, N, PAX (17.5-22.5ml)		E & N & CMI (25-30ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X										
Urinalysis bHCG (women only)	X	(X)			X						
Nasal swab/ saliva	X (V1-96 hours)	X	X	X	X	X	X	X	X	X	X

- Visit 5 to Visit 7 are scheduled relative to when the 2nd dose of vaccine/placebo (Visit 4) has been administered.

[§] Screening informed consent form (ICF).
[¥] Full study participation informed consent form, if remain eligible after completion of screening procedures.

[#] Vital signs includes pulse, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay, PAX= PAXgenes.

Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E =Elisa; Cyt= Th1 and Th2 cytokine profile; N= neutralization and/or pseudo-neutralisation assay; CMI= cell-mediated immunity assay, PAX= PAXgenes.

Blood test summary:

- Screening: Safety bloods (Full Blood Count, FBC; Urea and Electrolytes, U&E; Liver Function tests, LFT); Screening bloods (HBsAg, HIV, Glycosylated hemoglobin; HbA1c), In group 3 only- CD4+ -lymphocyte count, CD4+ & VHIV-1 viral load, VL)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 3 Safety bloods (FBC, U&E, LFT)
- Visit 4 Immunogenicity- Elisa & cell-mediated immunity
- Visit 5 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Visit 6 NIL
- Visit 7 Safety bloods (FBC, U&E, LFT), Immunogenicity- Th1 and Th2 cytokine profile
- Visit 8 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay & cell-mediated immunity
- Visit 9 Safety bloods (FBC, U&E, LFT), Immunogenicity- Elisa
- Visit 10 Immunogenicity- Elisa
- Visit 11 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assays
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days.

Table 10: Visit schedule, group 2b (extended efficacy cohort; remaining 1650 participants)

Visit number	Screening	V1	V2	V3	V4	V5	V6	COVID-19
Day #	-14 to -1	0 (Vax1)	28 (Vax2)	42	56	182	364	Illness
	Screening	D0	Visit 1 + 28 days ±7	V2+14 days ±3	V2 +28 (±7)	D182 (±14)	D364 (±14 days)	As required [$]
Eligibility	X	X						
Consenting	X[§]	X[¥]						
Inclusion/ exclusion	X	X	X					
Contraindications	X	X	X					
Vital signs [#]	X	X	X	X	X	X	X	X
Medical history	X							X
Physical examination	X (full)	X	X (full)	X	X	X	X	X (full)
Vaccination		X	X					
Post vaccination observation		X	X					
Diary cards provided		X	X					X (illness DC)
DC collected			X					
Screening bloods (HBsAg, HIV, HbBA1C)	X						X (HIV)	
Immunology bloods***		E (10-15ml)	E, N, HLA (17.5-22.5ml)	E & N (15-20ml)	E (10-15ml)	E (10-15ml)	E & N (15-20ml)	E (10-20ml)
Urinalysis	X							
Urinalysis bHCG (women only)	X	(X)	X					
Nasal swab/ saliva	X (V1-96 hours)	X	X	X	X	X	X	X

[§] Screening informed consent form (ICF).
[¥] Full study participation informed consent form, if remain eligible after completion of screening procedures.

* IF participants receive two doses of vaccine, then dose 2 will be administered at Visit 2, and follow up visits will be completed 14 days post dose 2 (6- visit schedule). IF participants only receive ONE dose of IP, then no vaccine will be administered at visit 2, and day 42 visit will not be included in visit schedule (5-visit schedule)
[#] Vital signs includes pulse, respiratory rate, oxygen saturation, blood pressure and temperature;

** Timeline is approximate only. Exact timings of visits relate to the day on enrolment, i.e., each visit must occur at indicated number of days after enrolment ± time window

***Abbreviations for laboratory tests: E=Elisa; Cyt=Th1 and Th2 cytokine profile; N=neutralization and/or pseudo-neutralisation assay; CMI=cell-mediated immunity assay.

Blood test summary:

- Screening: Screening bloods (HBsAg, HIV, HBA1C)
- Visit 1: Immunogenicity- Elisa
- Visit 2 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay and HLA
- Visit 3 Immunogenicity- Elisa, neutralization and/or pseudo-neutralisation assay
- Visit 4 Immunogenicity- Elisa
- Visit 5 Immunogenicity- Elisa
- Visit 6 Immunogenicity- Elisa & neutralization and/or pseudo-neutralisation assay
- Illness visit Immunogenicity- Elisa

$ Nasal swabs/ saliva and Elisa (illness) will be repeated at Days 5-8, 12-15 and 28-35 days

7.4.7. 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.

7.4.8. 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.

7.4.9. 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 >14 days and >21 days after the first dose.

Secondary VE analyses will also include stratification to evaluate VE for COVID-19 due to the N501.V2 (also known as 20C/501.V2 or B.1.351 lineage)

a. VE in preventing virologically-confirmed COVID-19 clinical disease irrespective of COVID-19 sero-status at randomization, and stratified by sero-status at randomization.

b. VE in preventing virologically-confirmed COVID-19 clinical disease occurring more than 14 days after a second dose for the overall population and those that were sero-positive at baseline.

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 (PCR+ at least one symptom of fever > 37.8oC, cough, shortness of breath, anosmia, aguesia).

i. VE against N501Y.v2 variant of the SAR-CoV-2 virus

10.4. Exploratory efficacy endpoints could include the following analyses at (i) >21 days following first dose of vaccine, (ii) >14 days after second dose of vaccine, (iii) for overall trial population, (iv) stratified for sero-status at randomisation [(seronegative at randomisation and PCR negative within 4 days of randomisation) and seropositive at randomisation]

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, 8th 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.

Summary of protocol amendments: Version 4.1 to version 5.0 24th November 2020 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 5.0, 24th November 2020

Section	Amendment made	Justification
Investigators	Mduduzi Masilela replaces Sherman Padayachee as principal investigator of Setshaba research centre	Sherman Padayachee has resigned. Mduduzi Masilela is approved as sub-investigator. Approval as principal investigator requested.
Monitoring contact	Addition of Kevin Shikanga as alternative contact for PPD	Nicolette Stott involved in other projects and Kevin Shikanga has taken over as project lead for PPD.
Introduction, rationale	Number of COVID-19 cases and deaths updated	Number of cases and deaths increased significantly globally since last amendment
7 Trial procedures 7.4.6 added	Addition of two-weekly contact with participants	COVID-19 case numbers increasing in South Africa since early November 2020. Regular contact with participants will allow for identification of possible cases, and participants will be asked to attend site for swab.
Appendix 2	Appendix 2: UCT CLII site specific procedures added.	UCT HREC requires UCT site specific procedures to be included in protocol.

Summary of protocol amendments: Version 5.0 to version 5.1 11th December 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 5.1, 11th December 2020

Section	Amendment made	Justification
Synopsis, Section 4: Objectives Section 10.3, 10.4	Clarification of secondary and exploratory efficacy objectives & endpoints. Analyses will be stratified according to participants' SARS-CoV-2 sero-status at randomization. Efficacy will be assessed at multiple time points after vaccination, including: >14 and >21 days after first/ only dose of vaccine and >14 days after second dose of vaccine	Vaccine Efficacy against disease is affected by number or doses and time after vaccination that participant is exposed to SARS-COV-2.

Summary of protocol amendments: Version 5.1 to version 6.0 15th January 2021

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 6.0, 15th January 2021

Section	Amendment made	Justification
Background	Update of numbers of cases and deaths. Included details of new SARS-CoV-2 variant	Pandemic has entered its second wave globally. A new variant of SARS-CoV-2 has been identified in South Africa
Objectives & 10.3	Secondary efficacy objectives will include stratification of analysis by variant of SARS-CoV-2	The new SARS-CoV-2 variant 501Y.V2 is the dominant strain circulating during the second wave of COVID-19 in South Africa. This trial is well placed to determine the efficacy of the vaccine against new variant.

Appendix 2: UCT CLII site specific procedures

1. Recruitment Strategies

University of Cape Town Lung Institute site:

Adults in Cape Town will be recruited by the following methods:

Recruitment from data bases at the UCT Lung Institute: CLII will utilize databases at the UCT Lung Institute of healthy participants who have previously has participated in clinical trials as controls. Only patients who have consented to allow telephonic contact to inquire on their interest to participate in future studies will be approached).

Recruitment using posters: Adverts approved by UCT HREC will be utilized and placed in health care clinics and other public places.

Recruitment using radio announcements: Community and talk radio stations will be used to recruit healthy individuals. Only wording that is approved by the UCT HREC will be utilised for this purpose.

Community-based recruitment: The CLII has partnered with the provincial authorities and is currently engaged in screening (symptomatic and asymptomatic) individuals for COVID-19 in communities of Mitchells Plain and Klipfontein district. This initiative is being conducted as part of the HREC approved XACT-COVID study (REF 204/2020) and is conducted synergistically with the provincial efforts in current "hotspots". Briefly, the CLII sets up a well ventilated mobile outdoor clinic at various pre-identified spots with in the Klipfontein and Mitchels Plain district (this is done in conjunction with the Provincial authorities).

We will leverage this collaboration to invite all asymptomatic participants meeting the "screening" inclusion and exclusion criteria (many of the inclusion and exclusion criteria for this protocol can be assessed at point of contact e.g. an inquiry about comorbidity, pregnancy, willing to use contraception, current symptoms, contact with a confirmed patient with COVID-19 etc.). The participants who are willing to participate will be give the ICF and requested to contact the study coordinator for scheduling a study visit.

Competitive recruitment will be undertaken across all South African sites in order to reach the targets as set out in the protocol. UCT will only contribute recruitment into group 2 and will aim to recruit up to 50 participants in group 2a and up to 288 participants in group 2b.

2. Vaccination

The administration of vaccine at the Cape Town site will take place by the trial doctor at E16 clinic at the division of pulmonology where a fully equipped emergency trolley with intubation facilities, supplemental oxygen resuscitation equipment and drugs are available (see resuscitation trolley SOP, check list of equipment and list of medication that is available). The administration of vaccine will be supervised by a Pulmonologist / Specialist physician with experience in ACLS techniques. Additionally, the Division of Pulmonology has clinics running on all days with a number of medical registrars, pulmonologists and nurses on the same floor (~20 meters) at any given time can be available to assist within seconds when required (administration of vaccine will only take place within clinic hours). Thus, making the vaccine administration process as safe as possible for our patients.