



agriculture, forestry & fisheries

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REPUBLIC OF SOUTH AFRICA

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APPLICATION FOR INTENTIONAL INTRODUCTION (CONDUCT A TRIAL RELEASE) OF GENETICALLY MODIFIED ORGANISMS (GMOs) INTO THE ENVIRONMENT OF SOUTH AFRICA

PART I (to be completed for all GMOs)

1. APPLICANT

1.1 Name of applicant

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1.2 Address of applicant

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2. BRIEF DESCRIPTION OF THE GMO

Provide a brief description of the GMO, the intended function(s) of the genetic modification(s), and the GM trait(s) of the GMO.

ChAdOx1 nCoV-19 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein with a leading tissue plasminogen activator (TPA) signal sequence.

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3. BRIEF DESCRIPTION OF THE PROPOSED TRIAL RELEASE

3.1 Provide a brief description of the proposed trial release.

The trial to be conducted in South Africa will enroll adults living without and with HIV to assess safety, immunogenicity and efficacy of one and two doses of ChAdOx1-nCoV-19. The South Africa study on ChAdOx1-nCoV-19 (Group 1 enrolment) will only be initiated following review by the Data and Safety Monitoring Committee (which will oversee both 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 will occur in tandem with opening of enrolment of the efficacy-cohort in the UK. The initial sample size

for the trial is expected to be 2800 research participants. The total duration of the study will be 12 months from the day of enrolment for all participants.

3.2 What is the aim of the proposed trial release of the GMO? Provide clear and detailed objectives for the trial release.

In adults without HIV (HIV-uninfected)

Primary objective:

To assess the safety of the candidate vaccine ChAdOx1 nCoV 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-1 disease cases that are naïve to SARS-CoV-2 infection at time of randomization.

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	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 severe and non-severe COVID-19	<p>The primary efficacy [objective] and endpoint include PCR positive COVID-19 disease cases occurring in participants that were sero-negative for SARS-CoV-2 (i.e. COVID naïve) at randomization.</p> <p>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:</p> <ol style="list-style-type: none"> 1. New onset systemic symptoms consistent with viral illness of at least two of the following: <ol style="list-style-type: none"> i. Fever or history of new-onset fever; ii. Cough; iii. Sore throat; iv. Myalgia; v. Ageusia; vi. Anosmia; vii. Headache; viii. Diarrhea <p>OR</p> <ol style="list-style-type: none"> 2. New onset lower respiratory tract disease (LRTI) (any): i. Tachypnea or dyspnea; ii. Low peripheral oxygen saturation (< 95%); iii. Presence of adventitious sounds (Crackles or bronchial breathing); iv. Radiographic findings consistent with LRTI <p>AND</p> <p>Positive SARS-CoV-2 specific reverse transcriptase polymerase chain reaction (RT-PCR)</p> <p>Secondary efficacy [objectives], endpoints in COVID-19-naïve persons (and for all patients) include:</p> <p>VE in preventing virologically-confirmed COVID-19 clinical disease; Per-protocol population (PPS) <i>analysis</i></p> <ul style="list-style-type: none"> ○ VE in preventing PCR positive COVID-19 disease cases (as per primary endpoint), but irrespective of sero-status for SARS-CoV-2 at randomization. ○ VE in preventing Severe virologically confirmed COVID-19 clinical disease, defined by NEWS-2 score >6 ○ VE in preventing LRTI associated with virologically-confirmed COVID-19 clinical disease ○ VE in preventing hospitalization due to virologically confirmed COVID-19 disease ○ VE in preventing death associated with virologically-confirmed COVID-19 clinical disease ○ VE in preventing] all-cause LRTI (overall and stratified by hospitalization or not, as well as by NEWS-2 score of >6), irrespective of test result for SARS-CoV-2.
Secondary objective (Group 1 and Group 2)	To assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19	<ol style="list-style-type: none"> 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.

In adults living with HIV (HIV-infected)

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 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. Exploratory immunology: a) Fc effector functionality b) Cell analysis by flow cytometry assays

4. CHARACTERISTICS OF THE HOST OR UNMODIFIED RECIPIENT ORGANISM

4.1 Specific and common names of the unmodified recipient or host organism.

ChAdOx1 (AdvY25)

4.2 Natural habitat, geographic distribution, geographic origin, and centres for diversity. Provide details on the type of environment and the geographical areas for which the plant is suited.

The wild type chimpanzee adenovirus isolate Y25 was originally obtained from William Hillis, John Hopkins University of Medicine. The virus was passaged in HEK293A cells (Invitrogen, Cat. R705-07) and purified by CsCl gradient ultracentrifugation.

4.3 Comment on whether or not the unmodified recipient organism or host has any adverse effect on:

4.3.1 Humans

Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US. In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titre neutralising antibodies to AdHu5, whilst only 4% had high-titre neutralising antibodies to ChAd63. Immunity to both vectors was age-dependent.

Adenoviruses are attractive vectors for human vaccination. They possess a stable virion so that inserts of foreign genes are not deleted. They can infect large numbers of cells and the transferred information remains extra-chromosomal, thus avoiding any potential for insertional mutagenesis. Replication defective adenovirus can be engineered by deletion of genes from the E1 locus, which is required for viral replication, and these viruses can be propagated easily with good yields in cell lines expressing E1 from AdHu5 such as human embryonic kidney cells 293 (HEK 293 cells)

4.3.2 Animals

None

4.3.3 Plants

None

4.3.4 Agricultural production

None

4.3.5 Any other aspect of the environment.

None

4.4 Reproduction:

4.4.1 Provide detailed information on the mode(s) of reproduction.

The ChAdOx1 (AdvY25) viral vector is replication-deficient as the essential E1 gene region - which is essential for viral replication - has been deleted. The virus is unable to replicate within vaccinated animals or humans.

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4.4.2 Provide detailed information on specific factors affecting reproduction.

The virus is unable to replicate within vaccinated animals or humans.

4.4.3 Provide detailed information on the generation time.

Not applicable. The virus cannot replicate.

4.5 Survivability in the environment:

4.5.1 Provide details on structures produced by the host or unmodified recipient for survival or dormancy.

Specific information on the survivability in the environment is not known, but the risk of the virus accessing the environment is negligible.

To note, the virus is incapable of surviving outside of a host cell and is susceptible to common disinfectants.

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4.5.2 Provide information on specific factors affecting survivability.

Not applicable, as noted above

4.6 Dissemination in the environment:

4.6.1 Provide details on how the the host or unmodified recipient may disseminate in the environment.

The use of the vaccine will be within a contained clinical trial environment and not for general release. As no biodistribution can occur within human subjects due to this being a non-replicating virus as detailed above, there is no risk of vaccinated humans spreading this product within the environment

4.6.2 Provide information on specific factors affecting dissemination.

The vaccines are supplied in sealed sterile vials. The vials are handled by trained pharmacists using aseptic technique. The administration of the vaccination to the research participant is via intramuscular route by trained medical staff. Administration of the vaccination follows standard safe medical technique. The injection site is cleaned prior to vaccination.

The research sites follow stringent procedures for the disposal of biohazardous waste.

4.7 Provide information on how the host or unmodified recipient is usually utilised in agriculture, forestry, medicine, or other areas.

The vaccine will be used in a controlled manner in a clinical trial environment at research sites approved to conduct the study by the South Africa Health Products Regulatory Authority (SAPRA) and the Wits Human Research Ethics Committee (WHREC). Only eligible research participants enrolled in the clinical trial will receive the vaccination.

5. BRIEF SUMMARY OF FIELD OR CLINICAL TRIALS UNDERTAKEN THUS FAR

5.1 Submit a list of previously authorised field or clinical trials undertaken by the applicant with the GMO in:

(a) South Africa

None at present

(b) Other countries

United Kingdom, Switzerland, Saudi Arabia

Your answers to (a) and (b) should include information on the country, year, location and the authority from which permission was obtained to run the field trials.

Please refer to tabulation of trials conducted in the various regions and the publication and clinical trial registry numbers.

5.2 For GM plants, provide a scientific summary of the field performance of the GM plant, including a scientific explanation of the efficacy of the introduced trait for each of the previously authorised activities listed in 5.1.

Not Applicable

5.3 For GMO vaccines, provide a scientific summary of the efficacy and results for each of the previously authorised activities listed in 5.1.

The phase I/II study in health adults in the UK, being initiated in late April 2020 will be the first-in-human study employing ChAdOx1 nCoV-19.

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 5×10^9 vp to 5×10^{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	Publication / Registration Number
					5×10^8 vp	3	Antrobus et al, 2014.

UK	FLU004	ChAdOx1 NP+M1	18-50	IM	5x10 ⁹ vp	3	Molecular Therapy. DOI: 10.1038/mt.2013.284 [12]
					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
		ChAdOx1 85A	18-50	IM	5x10 ⁹ vp	6	Wilkie et al, 2020 Vaccine

UK	TB034				2.5x10 ¹⁰ vp	12	DOI: 10.1016/j.vaccine.2019. 10.102 [14]
		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 and	TB039 (ongoing)	ChAdOx1 85A	18-55	Aerosol	1x10 ⁹ vp	3	Clinic altrial s.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	Clinic altrial s.gov: NCT03681860
					2.5 x10 ¹⁰	6	

UK	VANCEO 1	ChAdOx1.5T4 MVA.5T4	18 – 75	IM	2.5x10 ¹⁰ vp	34	Clinic altrial s.gov: NCT0 2390
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Country	Trial	Vaccine	Age	Route	Dose	Number of Participants (Received ChAdOx1)	Publication / Registration Number
UK	ADVA NCE (ongo ing)	ChAdOx1.5T4 MVA.5T4	≥18	IM	2.5x10 ¹⁰ vp	23 (as of Feb 20)	Clinicaltrials. gov: NCT0381594 2
UK	VAC067	ChAdOx1 LS2	18-45	IM	5x10 ⁹ vp	3	Clinicaltrials. gov: NCT0320342 1
					2.5x10 ¹⁰ vp	10	
UK	VAMBO X	ChAdOx1 MenB.1	18-50	IM	2.5x10 ¹⁰ vp	3	ISRCTN46336916
					5x10 ¹⁰ vp	26	
					5x10 ⁹ vp	6	Clinicaltrials. gov:

UK	CHIK001	ChAdOx1 Chik	18-50	IM	2.5x10 ¹⁰ vp	9	NCT0359039 2 DOI: https://doi.org/10.4269/ajtmh.abstract2019 Abstract #59, page 19.
					5x10 ¹⁰ vp	9	
UK	ZIKAO01 (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	MERS 001 (ongoing)	ChAdOx1 MERS	18-50	IM	5x10 ⁹ vp	6	Clinicaltrials.gov: NCT03399578 DOI: https://doi.org/10.4269/ajtmh.abstract.2018 Abstract#973, page 305. Folegatti et.al. 2020, Lancet Infect.Dis, <i>In press</i> .
					2.5x10 ¹⁰ vp	9	
					5x10 ¹⁰ vp	9	
					2.5x10 ¹⁰ vp (homologous prime-boost)	3	
Saudi Arabia	MERS 002 (ongoing)	ChAdOx1 MERS	18-50	IM	5x10 ⁹ vp	4	Clinicaltrials.gov: NCT04170829
					2.5x10 ¹⁰ vp	3	
					5x10 ¹⁰ vp	-	

6. INSERTED OR DELETED NUCLEIC ACID SEQUENCES AND THE GMO

6.1 Scientific and common names of the donor organism(s).

Chimpanzee adenoviruses

6.2 Natural habitat, geographic distribution, geographic origin, and centres for diversity of the donor organism(s).

Equatorial Africa

6.3 Provide a description of the methods used for genetic modification and, in cases where vectors were used, describe the nature and source of the vectors used.

Response combined for 6.3-6.6

6.4 Provide detailed information on the genetic construct and the region intended for insertion, including the source of donor DNA and the size and intended function of each constituent fragment of the region intended for insertion. Use maps and tables as appropriate. Provide information on any change in the ability of the GMO, which is the focus of this application, to transfer genetic material to bacteria, plants, or other organisms.

6.5 Provide information on the sequences actually inserted or deleted in the GMO:

6.5.1 The copy number of all inserts, both complete and partial.

6.5.2 In the case of deletion(s), the size and function of the deleted region(s).

6.5.3 Location(s) of insert(s) (nucleus, chloroplasts, mitochondria, or maintained in non-integrated form), and the molecular methods used for determination of the location(s).

6.5.4 Provide information on the genetic stability of the inserted sequences.

6.6 Describe the trait(s) and characteristics which have been introduced or modified:

6.6.1 Identify all inserted sequences and genes in the GMO.

6.6.2 Describe the gene products that are derived from the inserted genes.

6.6.3 Describe the biological activity associated with the inserted sequences.

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6.7 Provide information on the expression of the inserted sequences/genes:

6.7.1 State whether expression is constitutive or inducible. In the case of inducible expression, discuss the induction conditions.

ChAdOx1 nCoV-19 expression is constitutive.

6.7.2 Provide information on the expression of the products of the inserted sequences or inserted genes in the GMO.

ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for Spike protein from the SARS-CoV-2 genome sequence accession MN908947.

6.8 Provide protocols for the detection of the inserted sequences or inserted genes in the environment.

Not applicable as the GMO cannot replicate and spread to the environment.

6.9 Provide information on how the GMO differs, or is expected to differ, from the host or unmodified recipient organism with regard to:

6.9.1 General traits.

6.9.2 Natural habitat and geographic distribution.

6.9.3 Reproduction.

6.9.4 Dissemination/dispersion, including persistence and invasiveness.

6.9.5 Survivability, especially in the spectrum of conditions which are likely to be found in the proposed release area(s) and surrounding environments(s).

6.9.6 The ability of the GMO to transfer genetic material to other organisms, including bacteria and plants.

Adenoviruses are attractive vectors for human vaccination. They possess a stable virion so that inserts of foreign genes are not deleted. They can infect large numbers of cells and the transferred information remains extra-chromosomal, thus avoiding any potential for insertional mutagenesis. Replication defective adenovirus can be engineered by deletion of genes from the E1

locus, which is required for viral replication, and these viruses can be propagated easily with good yields in cell lines expressing E1 from AdHu5 such as human embryonic kidney cells 293 (HEK 293 cells)

The prevalence of immunity to human adenoviruses prompted the consideration of simian adenoviruses as vectors. They exhibit hexon structures homologous to that of human adenoviruses. Indeed, ChAd63 hexons are most similar in sequence to the hexons of AdHu4, previously used by the US military in mass vaccination campaigns where over 2 million adults received tablets of serially passaged adenovirus with good safety and efficacy data.

There is no biodistribution and subsequent risk of this GMO spreading to the environment.

6.9.7 Adverse effects on:

6.9.7.1 Humans

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 volunteers 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.

6.9.7.2 Animals

None

6.9.7.3 Plants

None

6.9.7.4 Agricultural production

None

6.9.7.5 Any other aspect of the environment

None

6.9.7.6 Other.

None

7. TRIAL RELEASE: GENERAL INFORMATION

7.1 Trial site location:

7.1.1 What is the location of the proposed field or clinical trial release site(s)?

1.	Respiratory and Meningeal Pathogens Research Unit (RMPRU) First Floor, Central Wing, Nurses Residence Chris Hani Baragwanath Academic Hospital, Chris Hani Road, Soweto Johannesburg, Gauteng, South Africa, 2013
2.	Setshaba Research Centre (SRC) 2088 Block H, Soshanguve 0152, Gauteng, South Africa
3.	Wits RHI Shandukani Research Centre 2 nd Floor, Hillbrow Health Precinct, Corner Esselen Street and Klein Street, Hillbrow Johannesburg, South Africa, 2001

7.2 What are the trial size and the quantity of the GMO that is to be released, and what are the arrangements for producing the GMO in the quantities required for the trial?

The planned number of research participants for this ChAdOx1 nCov-19 study at the three South African sites will be 2800

The number of ChAdOx1 nCov-19 vaccine vials required for the clinical trial is estimated at 6720 vials.

The ChAdOx1 nCov-19 study vaccine vials production has subcontracted by the University of Oxford to Advent, a Good Manufacturing Practice approved facility based in Italy. The facility was confirmed to have the capacity for mass production of the vaccines.

7.3 What are the arrangements for transporting the GMO to the release site?

The vaccines will be shipped by air to South Africa packaged on dry ice in order to preserve the cold chain management of the vaccines. Temperature monitoring devices will be included within the shipment to confirm and verify the cold chain management of the transport of the vaccines. A reputable courier proficient in the transport of Investigational Product will be used. The vaccine shipments will be transported to the respective approved research units via road. The transport of the vaccines will be in accordance with International Air Transport Association (IATA) requirements. All personnel within the custody chain of the vaccine shipment are trained in IATA regulations including the handling of biohazardous material.

7.4 What is the planned duration of the field or clinical trial and the reason for the desired duration?

The study is planned to start 1 June 2020 – 30 Nov 2021. This is anticipated duration of the study as per Protocol ChAdOx1 NCoV-19

7.5 Provide information on the experimental design for the field or clinical trial.

This is a Phase I/IIa, double-blinded, placebo-controlled, individually randomized study in adults aged 18-55 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 study will assess safety, immunogenicity and efficacy of one and/or two doses of ChAdOx1 nCoV-19. We will employ an adaptive study design, particularly for the efficacy cohort (Group 2, HIV-uninfected adults), in whom the dosing schedule is contingent on the immunogenicity results from the initial UK immunogenicity cohort (analysis will precede initiation of Group 2 in this study) which will determine whether a single or two dose schedule will be used in the UK and South African efficacy cohort (Group 2). For Group-1 and Group-3 (HIV-infected adults), a two dose schedule spaced 25-35 days apart will be evaluated for safety and immunogenicity. Furthermore, based on the force of infection and accrual of symptomatic COVID-19 cases in Group-2, the study may expand the number to be enrolled into the efficacy cohort to accrue sufficient number of endpoints to analyses for efficacy of at least 70% (and a lower bound of 10%) and 80% power (see sample size section).

The three trial groups with an overall initial sample size of 2800. Randomisation will take place at an intervention to placebo ratio of 1:1 in blocks of 10 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, and once approval to continue enrolment is issued, participants will be enrolled in parallel into Groups 2 and 3.

Participants will be followed over the duration of the study to record adverse events and episodes of virologically confirmed symptomatic COVID-19 cases. Participants will be tested for COVID-19 if they present with a new onset of at least two of the following symptoms: fever, cough, headache, myalgia, ageusia, anosmia, sore throat, chest pains/shortness of breath.

Moderate and Severe COVID-19 disease will be defined using clinical criteria. Detailed clinical parameters will be collected from medical records (or examination by study-staff) and aligned with agreed definitions of severity as they emerge. These are likely to include, but not limited to, 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.

Safety will be assessed in real time and monthly interim reviews are scheduled after Group 1 (50 HIV-uninfected) participants received the IP (dose 1 and dose 2 if given), after enrolment of 50 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).

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8. HUMAN AND ANIMAL HEALTH AND PATHOGENICITY

8.1 Will the GMO or its products enter the human or animal food chains as part of the field or clinical trial experiments?

8.1.1 If no, what measures will be taken to prevent human or animal ingestion of the GMO (if relevant)?

The vaccine will be administered by intramuscular injection. The vaccination of research participants will be performed within a controlled environment. Access to the research pharmacy is restricted to authorised personnel. The research protocol has stringent measures to control receipt of the vaccine. Research participants do not handle the vaccine. The research staff administers the vaccine to the research participant. A band-aid is applied over the vaccination site to mitigate any vaccine liquid leakage. There is no risk of accidental ingestion.

8.1.2 If yes,

(a) Provide information on the toxicity to humans and animals of the newly expressed protein(s) (including any marker proteins) or new constituents other than proteins.

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(b) Provide information on allergenicity to humans and animals of the newly expressed protein(s) (including any marker proteins).

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- 8.2 What are the implications of the proposed trial release activity with regard to the health and safety of the workers, cleaning personnel and any other person that will be directly or indirectly involved in the activity? Please take into consideration the provisions of the Occupational Health and Safety Act, 1993 (Act No. 85 of 1993 as amended by Act No. 181 of 1993) (and accompanying regulations) and indicate the proposed health and safety measures that would be applied.**

The vaccines are supplied in sterile, sealed vials. The handling of the vaccines is restricted to authorised, trained, pharmacists at the respective research units. The vaccines are prepared for administration using aseptic technique. The pharmacists involved in the preparation of the vaccine wear gloves and masks. Biohazardous waste disposal units are available in the pharmacy and in the clinic area when the vaccines are administered.

The injection site is covered with a band-aid after vaccination.

All staff receive training in health and safety in accordance with local country requirements.

Additional safety measures will be instituted during the COVID-19 pandemic period.

9. ENVIRONMENTAL IMPACT AND PROTECTION

- 9.1 What evidence is there concerning the transferability of the inserted nucleic acid sequences to other organisms in the release site and surrounding environment? If transferable, provide information to which organisms and at what frequencies the inserted nucleic acid sequences is transferable?**

This is a non-replicating vaccine vector. No environmental impact.

- 9.2 What evidence is there concerning the likelihood of spread/dissemination of the GMO outside of the release site or host organism?**

The research study and use of the vaccine is in a controlled environment. The vaccines are stored in restricted access research pharmacy units with maximum security measures instituted for the respective research unit. It is highly unlikely for the spread of the GMO outside of the approved research unit.

- 9.3 What data are available to suggest that the introduced nucleic acid sequences have no deleterious effect in the long term upon the species into which it has been introduced or to related species or any other organisms or to the environment in general?**

Toxicology studies on the ChAdOx1 nCoV-19 have not been performed to date. However, a mice study has been previously conducted on the

ChAdOx1 MERS vaccine, which is a ChAdOx1 vectored MERS-CoV vaccine expressing the full-length Spike protein. During the study, clinical condition, bodyweight, food consumption, haematology, blood chemistry, organ weights, macropathology and histopathology investigations were assessed. There were no unscheduled deaths in the study. There were no clinical signs considered clearly related to treatment with ChAdOx1 MERS and there was no apparent reaction to treatment at the dose site. Administration of ChAdOx1 MERS was associated with treatment related changes in the right lumbar lymph node, spleen and intramuscular injection site. The spectrum and severity of the changes were consistent with the administration of an antigenic substance such as ChAdOx1 MERS, and were considered to be non-adverse

9.4 Is the GMO intended to modify the characteristics or abundance of other species? If so, what are the target species and intended consequences?

No. The intention is not to modify the characteristics of other species. The intention is to use the vaccine in a controlled research environment to assess safety, immunogenicity and efficacy of the vaccine.

9.5 Detail any effects, especially long-term, that the trial release of the GMO is likely to have on the biotic and abiotic components of the environment. The answer should consider effects on general ecology, ecosystems, biodiversity, environmental quality, pollution in the area, non-target organisms, human/animal/plant health, and genetic resources (e.g. susceptibility of economically important species to biocides).

The vaccine is not intended or expected to be transferred to the environment.

9.6 What are the consequences of the GMO remaining in the environment beyond the planned period?

The vaccine is not intended to be placed in the environment.

10. MONITORING AND RISK MANAGEMENT PLAN

10.1 Provide a detailed supervision / monitoring and risk management plan that would be implemented for the trial release. The plan should include information on arrangements for storing the GMO in preparation for the trial release, for handling the GMO during the trial release, and for the monitoring of potential hazardous or deleterious effects that may result from the trial release of the GMO.

Each research unit has written procedures in the handling and management of GMO vaccines at the respective research unit. The GMO

vaccines are received by trained pharmacy staff. The GMO vaccines are handled in an aseptic manner. GMO vaccines received are checked for condition on receipt, cold chain management during transport meets the requirements of the GMO vaccine storage temperature and will be stored at the restricted access pharmacy according to the required storage conditions. Storage conditions will be continuously monitored. The GMO vaccines will only be administered to research participants who were confirmed eligible to participate in the study according to the research study randomization methods. The GMO vaccine will be handled and prepared using aseptic technique by trained pharmacy staff. Used vials will be disposed of in a biohazardous waste disposal unit. The GMO vaccine will be administered by research staff qualified by training and experience following site occupational safety procedures. In the COVID-19 environment staff will be equipped with personal protection equipment in accordance with local requirements. The used syringe will be disposed of in a biohazardous waste disposal unit. A band-aid will be applied to the injection site.

At the end of the study, all used and unused GMO vaccine vials will be reconciled and disposed of following approved biohazardous waste disposal processes. The documentation of the safe destruction of the GMO vials will be filed in the Trial Master File. All documentation associated with the shipment, receipt, dispensing, administration, disposal and destruction will be documented and records will be filed in the Trial Master File.

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10.2 Please specify the provisions to remove the GMO from the test site or any other place where it may be found upon completion of the trial release and to restore the test site and any such other place to its original form.

Disposal and Contingency Procedures

- Once thawed, vaccine-product cannot be refrozen and must not be re-used. All used and unused vaccine-product will be maintained at the study site in the designated freezer until the end of the trial and until the data have been cleaned and screened and the study file is frozen.
- Used syringes and needles are to be handled as any other sharp or biohazard and disposed of properly, as done with material used to provide a person with any other vaccine. Sharps containers are available in each designated vaccination area
- If necessary and required by sponsor, the used vaccine-product syringes may be stored in a separate space from unused vaccine-product syringes; the used vaccine-product syringes need to be sealed so as not to pose any greater risk than do unused vaccine product syringes. A small amount of vaccine volume may be present in used vaccine product syringes.

- Once the study file has been declared frozen the Sponsor will provide written authorization to return all unused vaccine-product to the manufacturer and to destroy all used syringes by incineration. This will be after all vials have been monitored for accountability. Destruction will be done by an accredited company such as Equilibrium Medical Waste Management.
- A log of returned and destroyed vials will be completed by the site pharmacist/ study-drug dispenser and maintained in a secure study file. A destruction certificate will be obtained for all destroyed vials and product
- All other materials that have been in contact with the vaccine or vaccination site on the skin must be punctually disposed of into sealed receptacles for incineration

VACCINE ACCOUNTABILITY:

The following standardised operating procedures is in place at site to ensure accurate vaccine accountability is kept:

- The pharmacist/ study-drug dispenser must record all stock received in the drug accountability logs and the pharmacy medication stock accountability log indicating date received, quantity received, batch number, expiry date and pharmacist's initials
- After the drug has been administered, the drug accountability log is completed by the pharmacist/study-drug dispenser.
- Date, visit number, quantity dispensed, expiry date, batch number, patient number, patient initials, time dispensed (if required), dispenser's initials and balance of drug are recorded.
- Once vaccines have been administered to participant; participant number, initials and vaccine date will be written on vaccine box, and vials/ syringes (without needles) returned to box as per specific protocol requirements.
- Used needles will be disposed of in biohazardous sharps containers and sent for incineration as medical waste
- Each numbered page of drug accountability log to be signed by investigator once full. If the study requires an unblinded pharmacist/dispenser then the sign off responsibility will be unblinded pharmacist/dispenser.

11. COMPLETE THE AFFIDAVIT. The affidavit is an inseparable part of the application form.

AFFIDAVIT

(To be completed in the presence of a Commissioner of Oaths)

I... Shabir Ahmed Madhi.....

ID-Number: 6611285196083..... Age 53 years.....

Residing address: 9 Colorado Road, Northcliff, 21151 Gauteng.....

Working address Chris Hani Road, CHBAH, New Nurses Residence, 1st Floor West Wing, Bertsham, 2013.....

Tel ...011-983-4266.....(w)(Fax) 0828706672.....(cell)

Declare under oath in English / confirm in English that: –


The information provided in the “APPLICATION FOR INTENTIONAL INTRODUCTION (CONDUCT A TRIAL RELEASE) OF GENETICALLY MODIFIED ORGANISMS (GMOs) INTO THE ENVIRONMENT OF SOUTH AFRICA” is to the best of my knowledge accurate and correct.

I am familiar with, and understand the contents of this declaration. I have no objection/have objection to taking the prescribed oath. I consider the prescribed oath as binding to my conscience.

Place: JOHANNESBURG.....

Date: 8 MAY 2020.....

Time: 12.30.....

Signature: .....

I certify that the above statement was taken from me and that the deponent has acknowledged that he she knows and understands the contents of the statement. The statement was sworn to/affirmed before me and deponent's signature/mark/thumb print was placed thereon in my presence.

At: Johannesburg on 8 May 2020 at 12:30.....

.....

Commissioner of Oaths

(Details to be provided on physical and postal address e.g. stamp of police station)

Force number/Rank/Name - print

COMMISSIONER OF OATHS
Brett Alan Crighton
Commissioner of Oaths Ex Officio
HUMAN RESOURCES MANAGER
ER24 HEAD OFFICE
1 Cambridge Manor Office Park
Cnr Witkoppen & Stonehaven Road
Paulshof, 2056, RSA
BC 8/5/2020

PART II (the section relevant to the GMO should be completed): **Not Applicable**

Section A: Trial release: GM crops or pasture plants

1. Provide information on how the GM plant differs from the recipient organism in general agronomic traits.
2. Reproduction and sexually compatible species:
 - 2.1 For pollen spread, identify pollinating agents and the distances to which pollen is known to spread from the GM plant.
 - 2.2 Provide details (including their distribution and proximity to trial release areas) on cultivated species that may become cross-pollinated with the GM pollen.
 - 2.3 Give details (including their distribution and proximity to trial release areas) of wild or indigenous species that may become cross-pollinated with the GM pollen.
 - 2.4 In the case of vegetative reproduction, describe methods to be used to limit vegetative spread of the GM plant into the environment.
 - 2.5 How do seeds of the GM plant interact in the environment and what long-term effects will the seed likely have on the environment?
3. If the foreign genes give rise to crops tolerant to agrochemicals, provide information on the registration of the agrochemicals to be used on the crop.
4. Provide information on registered agrochemicals that can be used to eliminate the crop from the environment.
5. Trial location:
 - 5.1 Provide one or more recent maps (aerial photo or orthophoto) at the appropriate scale with the trial site(s) marked.
 - 5.2 Provide a description of each field trial site in terms of:
 - 5.2.1 Size
 - 5.2.2 Soil
 - 5.2.3 Groundwater level
 - 5.2.4 Topography
 - 5.2.5 Flora and fauna, with special consideration of threatened or endangered species
 - 5.2.6 Climate, especially prevailing winds
 - 5.2.7 Former use and history of the site
 - 5.2.8 Distance from the nearest human settlements, along with the size of such settlements
 - 5.2.9 Distance from surface waters, and

5.2.10 Distance from listed ecosystems, critical biodiversity areas, and protected areas. In addressing this section, the Biodiversity GIS (BGIS) website (<http://bgis.sanbi.org/news.asp#newtools>) may be of use.

- 5.3 Provide a description of the environment immediately surrounding the trial release site. In addition, provide a map indicating the trial site and the location of, and distance to, nearby (within 3 km) structures (e.g. fences, roads, and buildings), landmarks, and crops.
- 5.4 Describe the barriers planned in order to segregate the experiments comprising the trial release from the surrounding environment.

Section B: Trial release: GMO vaccines

- 1. Provide details on the pathogenicity of the GMO vaccine, including evidence from the use of the host vaccine organism or other GMOs having the same host vaccine organism in present vaccines either in use or under development.**

Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US (Investigator Brochure Ref Nr. 15). In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titre neutralising antibodies to AdHu5, whilst only 4% had high-titre neutralising antibodies to ChAd63. Immunity to both vectors was age-dependent (Investigator Brochure Ref Nr 16).

- 2. Based on data obtained in contained experiments (please supply experimental data or references), what are the effects expected when the GMO vaccine interacts with non-target species?**

No effects are expected on non-target species due to the fact that this virus is unable to replicate and distribute within the vaccinated subject.

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- 3. In the case of human clinical trials, what is the likelihood that the live GMO vaccine may infect immunocompromised individuals in the population and how pathogenic would the GMO vaccine be in such individuals?**

Whilst 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

As noted above, Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US (15). In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titre neutralising antibodies to AdHu5, whilst only 4% had high-titre neutralising antibodies to ChAd63. Immunity to both vectors was age-dependent

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 GMO vaccine.

4. Provide details on safety and tolerability studies undertaken on the GMO vaccine, including toxicology and biodistribution.

Biodistribution of replication deficient simian adenoviruses

Biodistribution studies have been performed with three recombinant viral vectored vaccines based on E1, E3-deleted simian adenovirus, as well as one human adenovirus 6 vectored vaccine.

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5. Provide details on allergenicity / hypersensitivity studies undertaken on the GMO vaccine.

No hypersensitivity studies have been performed to date
Serious allergic reactions including anaphylaxis may occur, as also with any vaccine. The incidence of this is unknown, but is estimated at one per 10^5 to 10^6 vaccinations. Volunteers should be vaccinated in a clinical area where Advanced Life Support drugs and equipment are immediately available for the management of serious adverse reactions.

6. What is the existing evidence regarding level and duration of immunity produced by the GMO vaccine in the target species?

This information is currently not known and is one of the primary objectives of this study.
Cellular immunogenicity of recombinant E1 E3-deleted ChAdOx1 was comparable to that of other species E derived chimpanzee adenovirus vectors including ChAd63, the first simian adenovirus vector to enter clinical trials in humans.

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7. In the case of a human clinical trial, provide details on any pre-clinical studies undertaken with the GMO vaccine.

ChAdOx1 nCoV-19 has been shown to be immunogenic in BALB/c and CD-1 mice.

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8. Provide details on the planned adverse events monitoring to be undertaken during the trial release.

Safety Oversight

The site investigators/study physicians/designated staff will be responsible for continuous close safety monitoring of all study participants and for alerting the National Principal Investigator. A daily diary card will be completed by participants to record any adverse reactions, and any unexpected or severe reactions will be reported to the study physician immediately via a 24 hour emergency telephone number. Regular study visits will be occurring for an extended period – up to one year after receiving the vaccine.

Routine Reviews by Principal Investigator

The study investigators will be responsible for continuous close safety monitoring of all study participants, and for alerting National Principal Investigator if concerns arise or if criteria for expedited submission of safety data are met.

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 Table for Grading the Severity for Healthy Adult and Paediatric Adverse Events. 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.

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.

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 will be 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.

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9. Provide details on the likelihood of integration of the GMO vaccine into the vaccinees' DNA.

There is no likelihood of this happening as the vaccine has been modified to not be able to replicate

- 10. Will the subjects carry live GMO vaccine at the end of the trial? If so, will they be likely to disseminate the live GMO vaccine to the general population?**

In the biodistribution studies performed for replication deficient simian adenoviruses, there was no evidence of replication of the virus or presence of a disseminated infection. The virus is unable to replicate within vaccinated animals or humans.

- 11. Are any challenge tests or other tests using virulent field strains to be carried out on vaccinated animals? If yes, provide details of the tests.**

No. The vaccines are intended for administration to human research participants.

- 12. Would the use of this GMO vaccine preclude the future use of the host vaccine organism for immunisation purposes?**

No. The use of this vaccine does not preclude the use of other vaccinations for immunization purposes.

- 13. What is the likelihood that any component of the GMO vaccine or the host vaccine organism would be used in other human or animal vaccines?**

There are no restrictions for the component of the vaccine to be used in other vaccines

- 14. How will you distinguish between the GMO and the GMO donor and recipient wild type organisms?**

All vaccine recipients will undergo testing for an immune response to the vaccine – the virus itself will not be tested as it cannot replicate. Immunogenicity will be assessed by a variety of immunological assays. This may include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma and flow cytometry assays, neutralising and other functional antibody assays and B cell analyses. Currently work is underway by WHO serology and COVID-19 vaccine groups to establish standardized assays that can be used across multiple sites. IgG serology assays for whole length spike protein and the RBD domain will be undertaken at RMPRU. In addition, samples will be sent to the Oxford collaborators group, and possibly InNexus Biotech Inc. for further testing.

- 15. What arrangements are proposed to dispose of waste containing any GMO vaccine either during the trial release or once the trial release is completed?**

Each research unit has written procedures in the handling and management of GMO vaccines at the respective research unit. The GMO vaccines are received by trained pharmacy staff. The GMO vaccines are handled in an aseptic manner. GMO vaccines received are checked for condition on receipt, cold chain management during transport meets the requirements of the GMO vaccine storage temperature and will be stored at the restricted access pharmacy according to the required storage conditions. The GMO vaccines will only be administered to research participants who were confirm eligible to participate in the study according the research study randomization methods. The GMO vaccine will be handled and prepared using aseptic technique by trained pharmacy staff. Used vials will be disposed of in a biohazardous waste disposal unit. The GMO vaccine will be administered by research staff qualified by training and experience following site occupational safety procedures. In the COVID-19 environment staff will be equipped with personal protection equipment in accordance with local requirements. The used syringe will be disposed of in a biohazardous waste disposal unit. A band-aid will be applied to the injection site.

At the end of the study, all used and unused GMO vaccine vials is be reconciliated and disposed of following approved biohazardous waste disposal processes. The documentation of the safe destruction of the GMO vials will be filed in the Trial Master File. All documentation associated with the shipment, receipt, dispensing, administration, disposal and destruction will be documented and records will be filed in the Trial Master File.

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PART III (to be completed for all GMOs)

COMMON FORMAT FOR RISK ASSESSMENT

(In accordance with Annex III of the Cartagena Protocol on Biosafety)

Risk assessment details	
1. Country Taking Decision:	South Africa
2. Title:	An adaptive phase I/IIa randomized 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.
3. Contact details:	Prof SA Madhi Respiratory and Meningeal Pathogens Research Unit (RMPRU) Chris Hani Baragwanath Academic Hospital Chris Hani Road, Soweto, Johannesburg, Gauteng, South Africa, 2013 Tel: +27 11 989 9891 Cell: +27 82 870 6672 Email: madhis@rmpru.co.za
LMO information	
4. Name and identity of the living modified organism:	ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1
5. Unique identification of the living modified organism:	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.)
6. Transformation event:	[Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]
7. Introduced or Modified Traits:	Medical products - Production of pharmaceuticals
8. Techniques used for modification:	[Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]
9. Description of gene modification:	[Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]
Characteristics of modification	

10. Vector characteristics (Annex III.9(c)):	This means the virus will not replicate in cells within the human body. [Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]
11. Insert or inserts (Annex III.9(d)):	[Confidential Information Deleted in accordance with section 68 of The Promotions of Access to Information Act, 2000]
Recipient organism or parental organisms (Annex III.9(a)):	
12. Taxonomic name/status of recipient organism or parental organisms:	ChAdOx1 nCov19
13. Common name of recipient organism or parental organisms:	ChAdOx1 nCov19
14. Point of collection or acquisition of recipient or parental organisms:	This is a genetically modified chimpanzee adenovirus
15. Characteristics of recipient organism or parental organisms related to biosafety:	No replication of the virus takes place after immunization
16. Centre(s) of origin of recipient organism or parental organisms:	The wild type chimpanzee adenovirus isolate Y25 was originally obtained from William Hillis, John Hopkins University of Medicine. The virus was passaged in HEK293A cells (Invitrogen, Cat. R705-07) and purified by CsCl gradient ultracentrifugation.
17. Centres of genetic diversity, if known, of recipient organism or parental organisms:	Unknown
18. Habitats where the recipient organism or parental organisms may persist or proliferate:	No replication of the virus takes place after immunization .
Donor organism or organisms (Annex III.9(b)):	
19. Taxonomic name/status of donor organism(s)	Chimpanzee/Simian adenoviruses

20. Common name of donor organism(s):	Chimpanzee/Simian adenoviruses
21. Point of collection or acquisition of donor organism(s):	Equatorial Africa
22. Characteristics of donor organism(s) related to biosafety:	Simian adenoviruses are not known to cause pathological illness in humans and the prevalence of antibodies to chimpanzee origin adenoviruses is less than 5% in humans residing in the US. In equatorial Africa (the natural habitat for chimpanzees), prevalence is higher but still below that to AdHu5. In a study in Kenya, 23% of children (aged 1-6 years) had high-titre neutralising antibodies to AdHu5, whilst only 4% had high-titre neutralising antibodies to ChAd63. Immunity to both vectors was age-dependent
Intended use and receiving environment	
23. Intended use of the LMO (Annex III 9(g)):	ChAdOx1 nCov19 vaccine is intended for use in a controlled clinical trial environment for study: An adaptive phase I/IIa randomized 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
24. Receiving environment (Annex III.9(h)):	<p>ChAdOx1 nCov19 vaccine will be used in a clinical trial at the following research units in restricted, secure environments:</p> <p>Research Unit1: Respiratory and Meningeal Pathogens Research Unit (RMPRU) 11th Floor, Central West Wing Chris Hani Baragwanath Academic Hospital Chris Hani Road, Soweto, Johannesburg, Gauteng, South Africa, 2013</p> <p>Research Unit 2: Setshaba Research Centre (SRC) 2088 Block H, Soshanguve 0152, Gauteng, South Africa</p> <p>Research Unit 3: Wits RHI Shandukani Research Centre 2nd Floor, Hillbrow Health Precinct, Corner Esselen Street and Klein Street, Hillbrow Johannesburg, South Africa, 2001</p> <p>The vaccines will be stored at -80°C in restricted access pharmacies at the respective sites noted above.</p>
Risk assessment summary	

25. Detection/Identification method of the LMO (Annex III.9(f)):

Immunogenicity will be assessed by a variety of immunological assays. This may include antibodies to SARS-CoV-Spike and non-Spike antigens by ELISA, ex vivo ELISpot assays for interferon gamma and flow cytometry assays, neutralising and other functional antibody assays and B cell analyses. Currently work is underway by WHO serology and COVID-19 vaccine groups to establish standardized assays that can be used across multiple sites. IgG serology assays for whole length spike protein and the RBD domain will be undertaken at RMPRU. In addition, samples will be sent to the Oxford collaborators group, and possibly InNexus Biotech Inc. for further testing.

26. Evaluation of the likelihood of adverse effects (Annex III.8(b)):

The following adverse events are expected to occur in some volunteers following vaccination with ChAdOx1 nCoV-19, based on previous experience with other simian adenovirus viral vectored vaccines.

- Injection site pain
- Injection site erythema
- Injection site warmth
- Injection site swelling
- Injection site pruritus
- Myalgia
- Arthralgia
- Headache
- Fatigue
- Fever
- Feverishness
- Malaise
- Nausea

These adverse events are expected to be primarily mild in severity, however occasional moderate or severe adverse events have been reported. These adverse events are expected to last for approximately 24-48 hours following vaccination, though adverse events of longer duration have also been reported

All vaccinations are administered intramuscularly. Anticipated adverse events are foreseeable on the basis of experience of using this and other similar adenoviral vectors extensively in clinical trials. When administered alone, intramuscularly, ChAdOx1 nCoV-19 is likely to induce injection site pain. Less frequent adverse events are likely to include erythema, swelling, itching and warmth. Local adverse events are likely to be mild in nature and should resolve rapidly, although there is the possibility of moderate or severe arm pain in some cases.

The common systemic adverse events, usually seen post viral vectored vaccines, include: headache, feverishness, myalgia, arthralgia, fatigue, malaise and nausea.

Volunteers would be expected to report a transient flu like illness within 24 hours of vaccination which should resolve completely within 48hrs. Given existing data for ChAdOx1 vectored vaccines in Oxford, it is anticipated that the majority of systemic adverse events post ChAdOx1 nCoV-19 will be mild in intensity. However, there is a possibility of moderate or severe systemic AEs.

As with any other vaccine, Guillain-Barré syndrome (GBS) or immune mediated reactions that can lead to organ damage may occur. However, such problems are very rare events with any vaccine and have never occurred with ChAdOx1 vectored vaccines or any other simian adenovirus to date.

Serious allergic reactions including anaphylaxis may occur, as also with any vaccine. The incidence of this is unknown, but is estimated at one per 10^5 to 10^6 vaccinations. Volunteers should be vaccinated in a clinical area where Advanced Life Support drugs and equipment are immediately available for the management of serious adverse reactions.

27. Evaluation of the consequences (Annex III.8(c)):	<p>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</p> <p>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 immediately the Investigators become 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>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.</p>
28. Overall risk (Annex III.8(d)):	<p>This is a non-replicating vaccine vector. There is no environmental risk involved.</p>

29. Recommendation (Annex III.8(e)):	None
30. Actions to address uncertainty regarding the level of risk (Annex III.8(f)):	Not Applicable
Additional information	
31. Availability of detailed risk assessment information:	The research study is continuously monitoring. Six monthly progress reports are submitted to the Regulatory Authorities reporting the progress of the clinical trial
32. Any other relevant information:	No
33. Attach document:	Not Applicable
34. Notes:	None