Project Brief: ChAdOx1 nCoV-19 Vaccine Trial

Full Title of Study/Programme	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.
Technical Focus Area	Research (Vaccine Preventable Diseases – Adults).
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 is still at an early stage of its COVID-19 outbreak, which is expected to start peaking toward the end of July 2020 but has already documented 3,500 cases and 58 deaths as of 22 April 2020 (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/II trial in healthy adults in the United Kingdom initiated recruitment in late April 2020. Data generated in the UK study will be used to support further larger phase II/III efficacy studies, which will include target groups at higher risk of severe disease. The trial to be conducted in South Africa will enrol adults living with and without HIV to assess safety, immunogenicity and efficacy of one and two doses of ChAdOx1-nCoV-19. The South African 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 expanded immunogenicity and "efficacy-cohort" in the UK.
Primary and Co-Primary Objectives	In adults without HIV (HIV-uninfected) To assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in healthy HIV-uninfected adults. To assess efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19, defined as virologically confirmed (PCR positive) COVID-19 disease cases that are sero-negative (naïve) for SARS-CoV-2 infection at time of randomization. In adults living with HIV (HIV-infected) To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV in people living with HIV. To evaluate the immunogenicity of ChAdOx1 nCoV-19 after first and second doses of vaccine.
Secondary Objectives	In adults without HIV (HIV-uninfected) To assess the immunogenicity of ChAdOx1 nCoV-19 in healthy HIV-uninfected adults. In adults living with HIV (HIV-infected) None as per the protocol.

Exploratory objective: HIV uninfected and HIV infected	In adults without HIV (HIV-uninfected) To assess B cell responses to SARS-CoV-2 spike trimer and/or the receptor binding domain. In adults living with HIV (HIV-infected) To assess B cell responses to SARSCoV-2 spike trimer and/or the receptor binding domain.
Primary Endpoint/Outcome	Group 1 and 2 (HIV Uninfected) 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; e) occurrence of serious adverse events; f) occurrence of disease enhancement episodes. Group 3 (HIV Infected) 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 e) occurrence of serious adverse events; f) occurrence of disease enhancement episodes. Group 2 (HIV Uninfected) The primary efficacy [objective] and endpoint include PCR positive COVID-19 disease cases occurring in participants that were seronegative for SARS-COV-2 at randomization based in a high sensitivity antibody test. 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: 1. New onset systemic symptoms consistent with viral illness of at least two of the following: i. Fever or history of new-onset fever; ii. Cough; iii.Sore throat;

	iv. Myalgia; v. Ageusia; vi. Anosmia; vii.Headache; viii. Diarrhea, ix. arthralgia, x. fatigue; xi. nasal congestion; xii. Nausea & vomiting; xiii. Chest pain/ shortness of breath; OR 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; AND Positive SARS-CoV-2 specific reverse transcriptase polymerase chain reaction (RT-PCR). Secondary efficacy [objectives], endpoints in participants who were SARS-CoV-2 sero-negative at randomization (and for all participants) include: i. VE in preventing virologically-confirmed COVID-19 clinical disease; Per-protocol population (PPS) analysis; ii. VE in preventing PCR positive COVID-19 disease cases (as per primary endpoint), but irrespective of serostatus for SARS-COV-2 at randomization; iii. VE in preventing Severe virologically confirmed COVID-19 clinical disease, defined by a NEWS-2 score of >6; iv. VE in preventing all-cause LRTI (per definition of the WHO ordinal scale for severity , as well as by NEWS-2 score of >6), irrespective of test result for SARS-COV-2; v. Severe disease/ LRTI/ hospitalization/ death as defined by WHO ordinal scale.
Secondary Endpoint/Outcome	Group 1 and 2 (HIV Uninfected) a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based micro-bead immunosorbent assay on luminex platform to quantify antibodies against SARSCoV-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 Group 2 (HIV Uninfected): 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. Group 3 (HIV Infected) a) Enzyme-linked immunosorbent assay (ELISA) or fluorescence based microbead immunosorbent assay on Luminex platform to quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates). b) Interferon-gamma (IFN-γ) enzymelinked 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 Group 3 (HIV Infected): 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.
Study Design	This is a Phase I/IIa, 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 study will assess safety, immunogenicity and efficacy of one and/or two doses of ChAdOx1 nCoV-19. It employs 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. In Group II (phase II; immunogenicity and efficacy cohort), the targeted accrual number is 1900 participants; this accrual number is needed to ensure a 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. Overall sample size is 2000, with a possible upward adjustment for efficacy endpoint. The planned sample size per group is 50 for Group 1, 1900 for Group 2, and 50 for Group 3. 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. Group 3 enrolment will either be in parallel to or follow on from group 1 enrolment. This decision will be guided by DSMC review of COV001 trial in the UK. Initiation of approval to continue enrolment into Group 2 and Group 3 will be contingent upon review by the joint DSMC of the ongoing study in the for the UK, which will inform whether and 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 cases. Participants will be tested for SARS-CoV-2 infection 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, diarrhea, arthralgia, fatigue, nasal congestion, nausea & vomiting throughout the duration of their participation. 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 the WHO Ordinal Scale for clinical improvement agreed definitions of severity as they emerge. These are likely to include measuring severity based on,

	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 a t least monthly interim reviews by the DSMC will be are scheduled after Group 1 participants received the IP (dose 1 and dose 2 if given), after enrolment of 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.
Study Population	Healthy adult participants that are HIV-uninfected (Groups 1 and 2); and generally, well people living with HIV [Group 3]); aged 18-65 years across both groups will be enrolled.
Study Sample Size	All groups: 2070 Group 1 = 50 Group 2a = 250 Group 2b = 1650 Group 3 = 100
Follow-up/Duration	The total duration of the study will be 12 months from the day of enrolment for all participants.
Study/Programme Sites	• Respiratory and Meningeal Pathogens Research Unit (RMPRU) • Setshaba Research Centre (SRC) • Wits RHI Shandukani Research Centre (SRC) • Perinatal HIV Research Unit (PHRU) • University of Cape Lung Institute and Centre for Lung Infection and Immunity (CLII) • Family Centre for Research with Ubuntu (FAMCRU) • SCTC
Completed Enrollment per site	• Respiratory and Meningeal Pathogens Research Unit (RMPRU) = 565 • Setshaba Research Centre (SRC) = 418 • Wits RHI Shandukani Research Centre (SRC) = 450 • Perinatal HIV Research Unit (PHRU) = 50 • University of Cape Lung Institute and Centre for Lung Infection and Immunity (CLII) = 240 • Family Centre for Research with Ubuntu (FAMCRU) =155

	• SCTC = 99
Study/Programme Duration	Approximately 14 months
National Principal investigator	Professor Shabir Madhi
Site Investigators	• Dr Lee Fairlie, Principal Investigator (Wits RHI) • Dr Faeezah Patel, Sub-investigator (Wits RHI) • Dr Maysseb Masenya, Sub-Investigator (Wits RHI) • Dr Elizea Horne, Sub-investigator (Wits RHI) • Dr Gabriella Benade, Sub-investigator (Wits RHI) • Dr Nadia Dawood, Sub-investigator (Wits RHI) • Alden Geldenhuys, Sub-investigator (Wits RHI) • Mrinmayee Dhar, Sub-Investigator (Wits RHI) • Tiffany Seef, Clinical associate (Wits RHI)
Other Partners & Collaborators	RMPRU Setshaba Research Centre Oxford Vaccine Group The Jenner Institute NICD
Sponsors	Wits Health Consortium (Pty) Ltd
Funders	• University of Oxford (Vaccine) • South African Medical Research Council • Bill & Melinda Gates Foundation
Publications/Key Presentations to Date	Nil
Progress Update as at June 2020	Screening and enrolments to begin June 2020. The target number of cases is 2070 across all groups and sites. The target enrollment number at WITS RHI Shandukani Research Centre is 450, majority being enrolled in Group 2.
Frequency of Donor Narrative Report	Annually
Overall Study/Project Contact	Dr Hermien Gous (hgous@wrhi.ac.za)
Briefing Owner and Date	Dr Hermien Gous October 2020 and Lee Fairlie June 2020