A Multi-Centre, Randomized, Double Blind, Phase 2b Trial to Evaluate the Safety and Immunogenicity of Janssen Ad26COVS1 (or mRNA (Moderna mRNA-1273 or Pfizer/BNT) and Novavax NVX-CoV2373 COVID-19 vaccines for Homologous and Heterologous Boosting in Adolescents and Adults Aged 12 to 64 Years with and without HIV infection in 3 African Countries (Kenya, Democratic Republic of Congo, and Rwanda).

Protocol Identification Number: VIBRI COVID-19-001/2021 (Amendment # 2)

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Funded by: Coalition for Epidemic Preparedness Innovation

Protocol #: VIBRI COVID-19-001/2021, Version: 3.0
Protocol Version Date: 16 January 2023

Protocol Amendment #: 02

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 1.3, 2.3, 3.1, 4.1, 4.2, 5.0 and 6.1.	Removed Janssen vaccine option as alternative booster vaccine and replaced with an mRNA (Moderna Mrna-1273 or Pfizer/BNT) vaccines for adolescents).	There is currently no information on safety and immunogenicity of the Janssen Covid-19 vaccine in adolescent/paediatric populations. As a result, the recommendation for use of the Janssen Covid-19 vaccine for primary or booster vaccination in adolescents/paediatric populations has not yet been made. Therefore, it's evaluation for booster vaccination in this study has been substituted with Pfizer or Moderna Covid-19 vaccines.
	Adolescent booster vaccination will be ≥5 months with no upper limit	This has been updated as per current US CDC and US FDA recommendations on booster vaccination for 12-17 years and to be consistent with the real-world setting. An overall and stratified immune analysis will be done by boost at ≥5-12 or >12 months.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP), applicable local regulatory authority guidelines. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Ethics Review Committee (ERC), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRC for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the Ethics Review Committee (ERC) before the changes are implemented to the study. All changes to the consent form(s) will be ERC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP (E6) guidelines.

Signature:  **Date:**

Dr. Lucas Otieno Tina, MD, MPH 16 January 2023
Principal Investigator

Signature:  **Date:**

Dr. Amos Ndhere, MD, MS 16 January 2023
Principal Investigator

1 PROTOCOL SUMMARY

1.1 SCIENTIFIC ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that emerged in the human population in Wuhan City, Hubei Province, China in December 2019. As of Jan 2022, there are over 328 million SARS-CoV-2 case worldwide and over 5.54 million deaths as a result of infection with SARS-CoV-2 (COVID-19). According to WHO Situation Report on 17 January 2022, Africa has 7 million confirmed cases with over 160, 804 deaths. The COVID-19 pandemic has caused global suffering, mortality, and severe economic pressures. There is thus a continued urgent global need to develop effective and safe vaccines and drugs to make them available at scale and equitably across all countries including in Africa.

Despite the rapid successes in vaccine development and issuance of WHO Emergency Use Listings (EUL), the WHO SAGE Interim Reports and FDA Emergency Use Authorization (EUA) for COVID-19 vaccine evaluations have reported limitations on safety and efficacy data in certain populations including children and adolescents, pregnant women, and immunocompromised individuals such as those with HIV/AIDS who are at higher risk of severe COVID-19 disease. Africa is especially vulnerable in this respect given the high prevalence of HIV/AIDS in countries such as Kenya where the prevalence is over 20% in some places.

The risk of recurring new waves of COVID-19 cases caused by Variants of Concern (VOC) exacerbate global public health crisis. A weak immune response to either single or two doses of primary vaccination against SARS-CoV-2 has been observed in immunocompromised population. Emerging data from observational studies consistently show waning immunity to primary vaccination for SARS-CoV-2 mutants, and a decline in vaccine effectiveness against SARS-CoV-2 infection and COVID-19 with time since primary vaccinations. These factors have led to consideration of the potential need for, and optimal timing of, booster doses for vaccinated populations. However, vaccine inequality, lack of availability of the same vaccine product used for primary vaccinations and unpredictable vaccine supply remain a challenge in LMIC. Consideration of heterologous COVID-19 vaccine to allow interchangeability (mix and match) use of vaccine products available in LMIC would therefore allow for programmatic flexibility.

Based on a recent systematic review and meta-regression analysis, across the four WHO EUL COVID-19 vaccines with the most data (i.e., BNT162b2, mRNA 1273, Ad26.COV2.S and ChAdOx1-S [recombinant] vaccine), vaccine effectiveness against severe COVID-19 decreased by about 8% (95% confidence interval (CI): 4-15%) over a period of 6 months in all age groups. In adults above 50 years, vaccine effectiveness against severe disease decreased by about 10% (95% CI: 6 – 15%) over the same period. Vaccine effectiveness against symptomatic disease decreased by 32% (95% CI: 11 – 69%) for those above 50 years of age. For some inactivated vaccines (CoronaVac and COVID-19 vaccine BIBP), WHO has already issued the recommendation for the administration of an *additional dose* to those aged 60 years or older as part of the primary series to make initial immunity more robust.

The FDA issued a EUA for the Janssen Ad26.COV.S1 COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. In September 2021, both the single dose and 2 dose Janssen COVID-19 vaccine regimens demonstrated high efficacy (79% protection

(CI, 77%-80%) for COVID-19-related infections and 81 percent (CI, 79%-84%) for COVID-19-related hospitalizations. vs 94% (CI, 58%-100%) protection against symptomatic COVID-19 in the U.S. respectively. Furthermore, the safety profile of the vaccine remained consistent and generally well-tolerated in the 2 regimens. Finally, when a booster of the Janssen COVID-19 vaccine given 6 months after the single shot, antibody levels increased nine-fold one week after the booster and continued to climb to 12-fold higher four weeks after the booster.

On June 14, 2021, Novavax reported the results of its PREVENT-19 pivotal Phase 3 trial of the NVX-CoV2373. The results showed an overall vaccine efficacy of 90.4% (95% CI: 82.9 – 94.6) in the US and Mexico. Sequenced data showed a vaccine efficacy was 93.2% (95% CI: 83.9 – 97.1) against Variants of Concern and Variants of Interest which represented 82% of cases. Studies of NVX-CoV2373 with Matrix-M adjuvant have demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age. On December 20, 2021, the WHO issued interim recommendations and authorized under its emergency use listing (EUL) procedure, the NVX-CoV2373 COVID-19 vaccine developed by Novavax and Serum Institute of India.

The pivotal phase 3 registration trial of the Moderna mRNA-1273 COVID-19 vaccine was conducted in the United States of America and involved about 30 000 participants aged 18 years or older with no known history of SARS-CoV-2 infection. Efficacy was evaluated for those subjects who received the second dose 21-42 days after the first dose. Vaccine efficacy (VE) was estimated as 94.1% (95% confidence interval (CI) 89.3–96.8%). In the phase 3 trial, the safety data supported a favorable safety profile. Reactogenicity symptoms, defined as solicited local injection site or systemic reactions during the seven days after vaccination, were frequent, mostly mild to moderate and short-lived after dosing for both adult age groups. The vaccine's AE profile did not suggest any specific safety concerns (WHO SAGE, 2021). The US CDC and FDA recommend that adolescents age 12 to 17 years old can receive a 3rd primary series at least 4 weeks after the 2nd dose and 4th booster shot at least 2 months after their last dose (CDC 2022).

The phase 2/3 pivotal registration trial of the BNT162b2 (Pfizer-BioNTech) vaccine was conducted at sites in six countries (Argentina, Brazil, Germany, South Africa, Turkey and the USA) and involved about 43 000 participants aged 16 to 85 years. The estimated vaccine efficacy (VE) was 94.6% (95% credibility interval (CI) 89.9–97.3%). Reactogenicity and adverse events associated with the vaccine were generally milder and less frequent in the older group (≥55 years of age) than the younger group (18–55 years of age) and tended to increase after the second dose. Reactogenicity was mostly mild to moderate and short-lived for both adult age groups (WHO SAGE, 2021). The WHO SAGE approved BNT162b2 (Pfizer-BioNTech) vaccines for children aged 6 months and older, having met the necessary criteria for safety and efficacy for administration (WHO SAGE, 2022). On 5th January 2022, the US CDC endorsed the Advisory Committee on Immunization Practices' (ACIP) recommendation to expand eligibility of booster doses to those 12 to 15 years old. CDC recommended that adolescents age 12 to 17 years old should receive a booster shot 5 months after their initial Pfizer-BioNTech vaccination series. ACIP reviewed the available safety data following the administration of over 25 million vaccine doses in adolescents; COVID-19 vaccines are safe and effective (CDC 2022).

The FDA and WHO have both recommended continued evaluation of vaccine effectiveness following issuance of a EUA and/or licensure which is critical to address the existing uncertainties, with high urgency to understand homologous and heterologous boosting, both for improved coverage of variants of concern and due to limitations of global vaccine availability. The VIBRI Consortium proposes to carry out a Multi-Centre Phase 2b RCT to evaluate the Safety and Immunogenicity of the Janssen Ad26COVS1, the Novavax NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines used as homologous and heterologous boost strategies among HIV positive adolescents and adults with a small control arm of HIV (-) participants. The trial will enroll up to 300 HIV (+) adolescents 12 to 17 years and about 1,650 adults aged 18 to 64 years (of which 1350 will be HIV (+) and 300 HIV (-), who have completed a primary series with a homologous vaccine series based on any one vaccine platform of a) mRNA (Moderna or Pfizer), b) adenovirus 26 (J&J) or c) inactivated (Sinopharm or Sinovac). These three have been the main vaccine platforms introduced across the three participating countries (Kenya, Democratic Republic of Congo and Rwanda) as of the current protocol. Participants must have completed the primary series at least 3 months prior to enrollment. In Stage 1, the booster vaccines will be evaluated in adult participants 18-64 years while in Stage 2, the booster vaccines will be assessed in adolescents 12-17 years of age.

Given the difference in vaccine rollout between countries, the timing of enrollment within each country is expected to stagger. All adult participants will be randomized 1:1 within their primary vaccine platform to receive either a single dose of Janssen Ad26COVS1 vaccine or Novavax NVX-CoV2373 COVID-19 vaccine between 5 and 7 months from completion of their primary series. All adolescent participants will be randomized 1:1 within their primary vaccine platform to receive either a single dose of Novavax NVX-CoV2373 COVID-19 vaccine or an mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccine ≥5 months after the primary series for adolescent participants. The booster vaccination interval for adolescents is consistent with new guidance from the US CDC/FDA and is reflective of real-world settings implementation of country MOH COVID-19 vaccination programs. Due to the uncertainty of vaccine supply and to allow for adequate capture of participants, the pre-booster vaccination enrollment period may vary anywhere from -85 days to 0 days till the time of boost (Day 0).

1.2 LAY SUMMARY

The Coronavirus (COVID-19 disease) is a worldwide illness that emerged in the human population in Wuhan City, Hubei Province, China in December 2019. As of Jan 2022, there are over 328 million SARS-CoV-2 case worldwide and over 5.54 million deaths as a result of infection with SARS-CoV-2 (COVID-19). According to WHO Situation report obtained 17 January 2022, Africa has 7 million confirmed cases with over 160, 804 deaths. The COVID-19 pandemic has caused global suffering, mortality, and severe economic pressures. There is therefore a continued urgent global need to develop effective and safe vaccines and drugs to make them available at scale and equitably across all countries including in Africa.

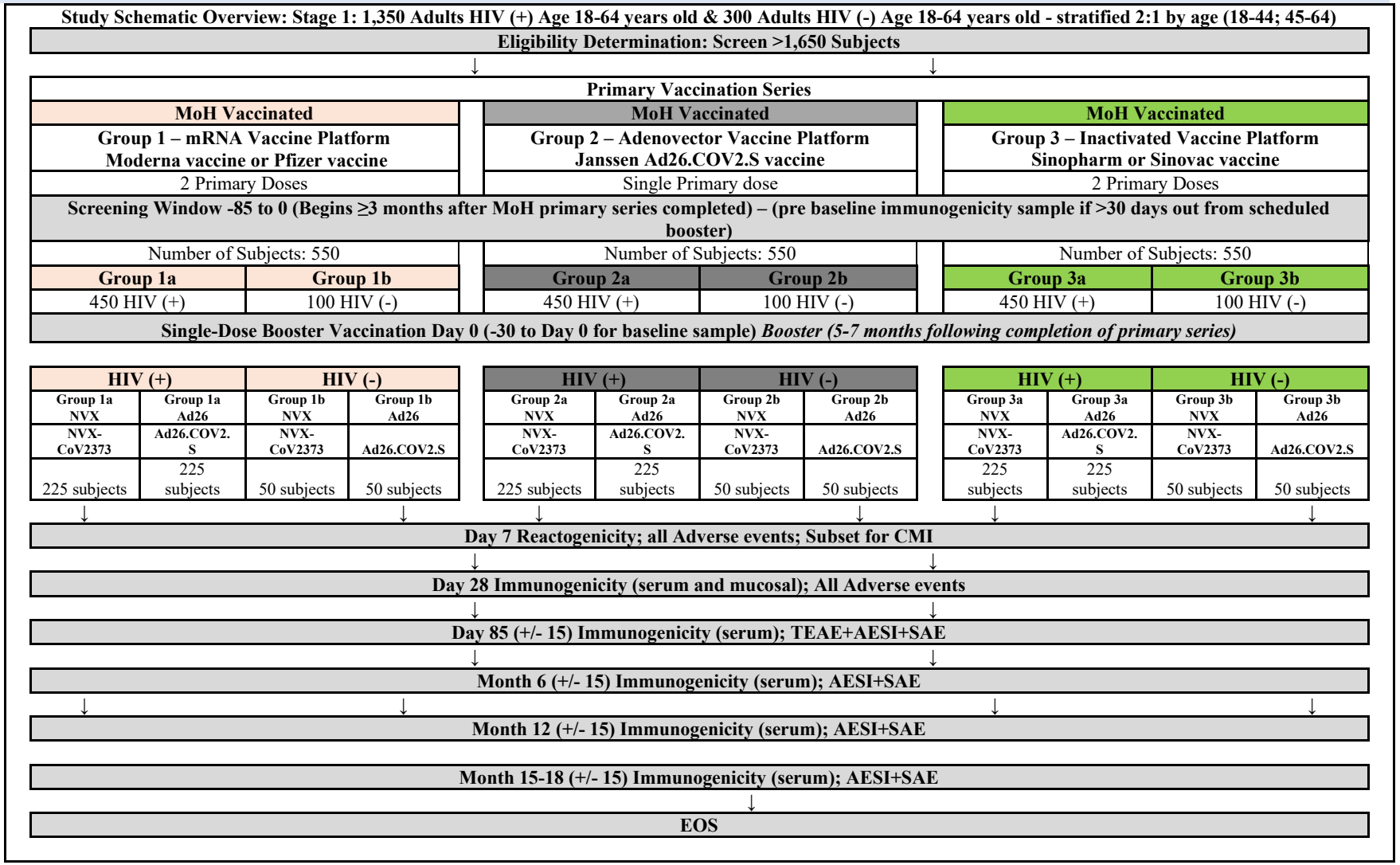
Despite the rapid successes in vaccine development, the WHO reports, and US Food and Drug Administration (FDA) reports written after assessing the COVID-19 vaccines for approval for Emergency Use, have shown that the COVID-19 vaccines require additional information which was not available from the big vaccine studies. For example, information on safety and how the primary and booster vaccines work in certain populations such as children and adolescents less than 18 years of age, pregnant women, and immunocompromised individuals like people with HIV/AIDS who are at higher risk of severe COVID-19 disease is required. Africa is especially at risk given the high number of HIV/AIDS patients in countries like Kenya where some places the rate of HIV infection is over 20% like in western Kenya.

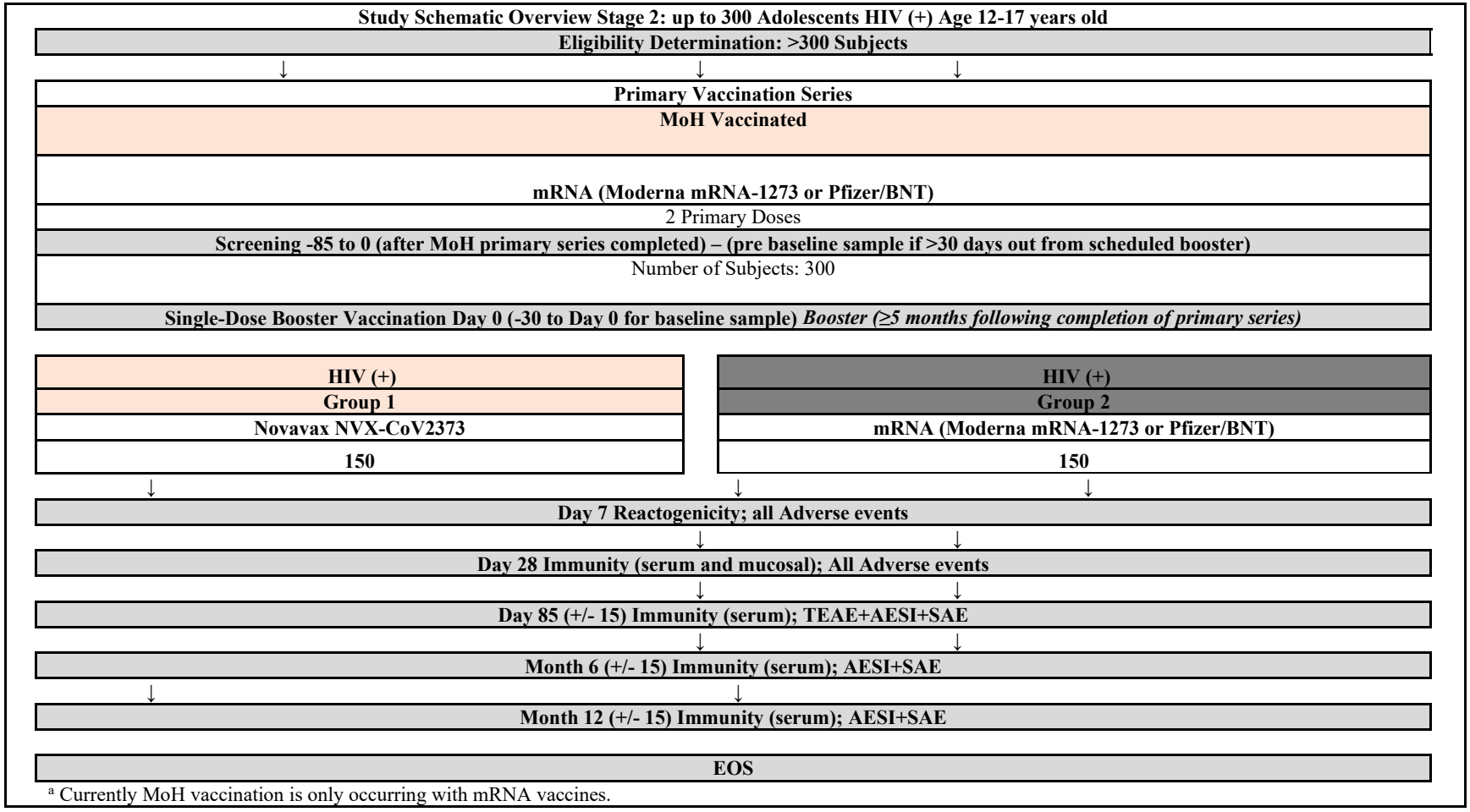
Emerging new COVID-19 variants of concern have led to new waves of COVID-19 cases worldwide and caused public health problems. Some studies suggest that some individuals, especially those with immunosuppression who received either a single dose or two doses of primary vaccination against COVID-19 developed only a weak immune response to the disease. Other studies have shown reducing immunity to primary vaccination against new cases of COVID-19 disease, and a declining vaccine effectiveness against COVID-19 from about 6 months after primary vaccinations. These factors have led to consideration of the need for booster doses for COVID-19 vaccinated populations.

A few studies have shown that some of the WHO approved COVID-19 vaccine are more effective when a mix and match primary and boosting schedules is used by reduction in the number of severe COVID-19 disease and hospital admissions. With emerging COVID-19 variants, vaccine constraints, and the need to achieve a broad immune response based on mix and match boosting strategies are currently being studied. A need for additional studies to assess how effective the vaccines in the context of heterologous boost in immunocompromised populations continue to be existing gaps in medical information. Because of limited supply of vaccines, lack of availability of the same vaccine product used for primary vaccinations and unpredictable vaccine supply in Low- and Middle-Income Countries (LMIC), use of COVID-19 vaccines to allow exchanged (mix and match) use of vaccines available in these countries would therefore address these challenges and allow flexibility within Ministry of Health vaccination programs.

The VIBRI Consortium which brings together researchers from Kenya, Rwanda and the Democratic Republic of Congo plan to conduct a Phase 2 vaccine study in these three countries to assess safety, mix and match booster vaccination schedule, how long the immune responses last after the booster and monitoring for new COVID-19 cases after vaccination.

1.3 STUDY SCHEMA





[a] Currently MoH vaccination is only occurring with mRNA vaccines.

1.4 SCHEDULE OF EVENTS (SOE)

Table 1: Study Schedule of Events

Activity	Screening Period	Treatment Period						
		Booster Vaccination & Follow-up Period (Days)				Follow up Period (months)		
Study Day/Month	**–85 to 0**	**0**	**7**	**28**	**85**	**6**	**12**	**15-18**
Window (days)	**7**	**0**	**+7**	**+7**	**+15**	**± 15**	**±15**	**± 15**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	x							
Demographics	x							
Vital Signs measurements (Temp, Heart Rate, Respiratory Rate & BP)[g]	x	x[a]x[b]	x	x	x	x	x	x
Medical history	x	x[a]						
Physical examination	x	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]	x[c]
Primary vaccination series recorded for SARS-COV-2	x							
Concomitant medications & vaccinations	x[d]	x	x	x	x	x	x	x
Urine pregnancy test (WOCBP)	x	x[a]						
FSH (if needed for post-menopausal status confirmation)	x							
HIV testing (2 mL)[k]	x							
HIV viral load, and/or CD4+ Cell Count (2mL) – for HIV (+) individuals	x					x	x	x
CBC, ALT, AST, Creatinine (4mL)	x							
Inclusion/exclusion criteria	x	x[a]						
Randomization		x[a]						
Adult Booster Vaccination (Janssen Ad26.COV2.S1/Novavax NVX-CoV2373)		x						
Adolescent Booster Vaccination (Novavax NVX-CoV2373 or mRNA (Moderna mRNA-1273 or Pfizer/BNT)		x[j]						
Immediate Reactogenicity[g]		x[b]						
Participant diary distribution (7-day diary)		x						
Participant diary review and collection[g]			x					
SARS-CoV-2 Rapid Antigen (Nasal Swab)		x[a]	x	x	x	x	x	x
Nasopharyngeal sample (PCR)[e]			x	x	x	x	x	x
Monitoring (passive surveillance) for COVID-19-like illness[h]		X						
COVID-19 daily diary self-directed diary (if		X						

rapid antigen test is positive)[i]								
Rapid positive SARS-CoV-2 retest or PCR		10-14 days after each (+) test						
Blood sampling for SARS-CoV-2 immunogenicity (ELISA) – IgG (5mL)	x[f]	x[a]		x	x	x	x	x
Blood sampling for SARS-CoV-2 neutralization antibody assay (10mL)	x[f]	x[a]		x	x	x	x	x
Mucosal Immunity (ELISA) – secretory IgA[j]		x[a]		x				
CMI-Subset (20 mL)[j]		x[a]	x					
Unsolicited AEs		x[b]	x	x				
TEAE attributed to vaccination		x[b]	x	x	x			
SAEs and AESIs		x[b]	x	x	x	x	x	x
End of Study (EOS) form completion							x[l]	x

Abbreviations: AE = adverse event; AESI = adverse event(s) of special interest; CD4 = cluster of differentiation; CMI=Cell Mediated Immunity; COVID-19 = coronavirus disease 2019; ELISA = enzyme-linked immunosorbent assay; FDA = United States Food and Drug Administration; HIV = human immunodeficiency virus; hACE2 = human angiotensin-converting enzyme 2; ID = identification; IgG = immunoglobulin G; TEAE = treatment emergent adverse event; PCR = polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] Pre-booster vaccination

[b] 30-60 min following vaccination (Prior to discharge from clinic). All Adverse Events (e.g., unsolicited, TEAE, SAE and AESI) will be collected from Visit 2 following randomization and booster vaccination.

[c] Symptom targeted

[d] Record concomitant medications or vaccinations received in last 30 days (inclusive of current medication)

[e] If SARS-CoV-2 rapid antigen test is positive for passive surveillance/unscheduled visits. In all participants for active surveillance from visit 3-8.

[f] If 6 month booster is planned for > 30 days after enrollment

[g] FDA toxicity grading to be applied for purposes of analysis but not clinical significance. In the case of vital signs in adolescents, only temperature will have FDA toxicity scoring applied.

[h] Subjects will be instructed to report any symptoms or exposure to SARS-CoV2 and be brought in for an unscheduled visit for SARS-CoV-2 Ag testing as well as scheduled testing.

[i] If SARS-CoV-2 Rapid Antigen test or PCR is (+) then subjects will be provided a COVID-19 illness symptom diary to be completed over 10 days. An Unscheduled visit will be performed at 10-14 days where SARS-CoV-2 Rapid Antigen or PCR retesting will be performed and diary reviewed. If subject remain symptomatic then another diary will be dispensed. If subjects remain symptomatic OR have a positive SARS-COV-2 rapid antigen test or PCR then they will return in another 10 days (unscheduled visit). Subject will continue to be followed until SARS-CoV-2 test is negative and subject is asymptomatic.

[J] Adults participants in Kenya only. No more than 60 HIV (+) and 30 HIV (-) participants within each primary vaccine platform will contribute to CMI testing based on subjects agreeing at the time of consent (opting in).

[K] HIV testing may be repeated at subsequent visits if clinically indicated but repeat not required per protocol.

[I] Adolescent follow-up period will be up to 12 months post booster vaccination.

[j] Monovalent or bivalent vaccines depending on MOH availability and supply.

1.5 PROTOCOL – KEY ROLES

KEY ROLES

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Country Principal Investigator - Rwanda	Vincent Mutabazi, MD MSc, Principal Investigator, Rinda Ubuzima & University of Rwanda Email: mutabazivincent@gmail.com
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Immunology Laboratory	CEPI Clinical Lab Network – ICDDR Bangladesh

Dr. Lucas Otieno Tina and Dr. Amos Ndhere as Principal Investigators at Victoria Biomedical Research Institute will be the study sponsors and will be responsible for the overall conduct of the trial, administrative actions between the VIBRI Consortium members, and oversight of study activities. They both led the development of the study protocol and will lead the statistical analysis and writing of the scientific report(s). All Clinical Investigators listed above will be responsible for the clinical conduct of the trial, the care provided to patients, oversight of field activities, and will contribute to the statistical analysis and writing of scientific report(s). See Appendix I for detailed roles and responsibilities for this study.

2 INTRODUCTION

2.1 BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that emerged in the human population in Wuhan City, Hubei Province, China in December 2019. As of Jan 2022, there are over 328 million SARS-CoV-2 case worldwide and over 5.54 million deaths as a result of infection with SARS-CoV-2 (COVID-19). According to WHO Situation report obtained 17 January 2022, Africa has 7 million confirmed cases with over 160, 804 deaths (1). The COVID-19 pandemic has caused global suffering, mortality, and severe economic pressures (2). There is therefore a continued urgent global need to develop effective and safe vaccines and drugs to make them available at scale and equitably across all countries including in Africa.

Despite the rapid successes in vaccine development, the WHO SAGE interim reports and FDA Emergency Use Authorization (EUA) for COVID-19 vaccine evaluations (3) have reported limitations on safety and efficacy data in certain populations including children and adolescents less than 18 years of age, pregnant women, and immunocompromised individuals such as those with HIV/AIDS who are at higher risk of severe COVID-19 disease. Africa is especially vulnerable in this respect given the high prevalence of HIV/AIDS in countries such as Kenya where the prevalence is over 20% in some places (4). In Kigali-Rwanda the prevalence estimate was 6% (5) and in the greater Kinshasa-DRC, prevalence was 11% (6).

The risk of recurring new waves of COVID-19 cases caused by Variants of Concerns (VOC) exacerbate global public health crisis. A weak immune response to either single or two doses of primary vaccination against SARS-CoV-2 has been observed in immunocompromised population (7). Emerging data from observational studies consistently show waning immunity to primary vaccination or SARS-CoV-2 mutants, and a decline in vaccine effectiveness against SARS-CoV2 infection and COVID-19 with time since primary vaccinations (8). These factors have led to consideration of the potential need for, and optimal timing of, booster doses for vaccinated populations (9). However, vaccine inequality, lack of availability of the same vaccine product used for primary vaccinations and unpredictable vaccine supply remain a challenge in LMIC. Consideration of heterologous COVID-19 vaccine to allow interchangeability (mix and match) use of vaccine products available in LMIC would therefore allow for programmatic flexibility.

Based on a recent systematic review and meta-regression analysis, across the four WHO EUL COVID-19 vaccines with the most data (i.e., BNT162b2, mRNA 1273, Ad26.COV2.S and ChAdOx1-S [recombinant] vaccine), vaccine effectiveness against severe COVID-19 decreased by about 8% (95% confidence interval (CI): 4-15%) over a period of 6 months in all age groups. In adults above 50 years, vaccine effectiveness against severe disease decreased by about 10% (95% CI: 6 – 15%) over the same period. Vaccine effectiveness against symptomatic disease decreased by 32% (95% CI: 11 – 69%) for those above 50 years of age. For some inactivated vaccines, WHO has already issued the recommendation for the administration of an *additional dose* to those aged 60 years or older as part of the primary series to make initial immunity more robust (10).

The FDA issued a EUA for the Janssen Ad26.COV.S1 COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older (11). In September 2021, both the single dose and 2 dose Janssen COVID-19 vaccine regimens demonstrated high efficacy (79% protection (CI, 77%-80%) for COVID-19-related infections and 81 percent (CI, 79%-84%) for COVID-19-related hospitalizations. vs 94% (CI, 58%-100%) protection against symptomatic COVID-19 in the U.S. respectively. Furthermore, the safety profile of the vaccine remained consistent and generally well-tolerated in the 2 regimens. Finally, when a booster of the Janssen COVID-19 vaccine given 6 months after the single shot, antibody levels increased nine-fold one week after the booster and continued to climb to 12-fold higher four weeks after the booster (12).

On June 14, 2021, Novavax reported the results of its PREVENT-19 pivotal Phase 3 trial of the NVX-CoV2373. The results showed an overall vaccine efficacy of 90.4% (95% CI: 82.9 – 94.6) in the US and Mexico. Sequenced data showed a vaccine efficacy was 93.2% (95% CI: 83.9 – 97.1) against Variants of Concern and Variants of Interest which represented 82% of cases (13). Studies of NVX-CoV2373 with Matrix-M adjuvant have demonstrated an acceptable safety and reactogenicity profile in adults ≥18 years of age. On December 20, 2021, the European Medicines Agency issued its authorization (14), the WHO issued interim recommendations and authorized under its emergency use listing (EUL) procedure for the Novavax NVX-CoV2373 COVID-19 vaccine (15).

The FDA and WHO have both recommended continued evaluation of vaccine effectiveness following issuance of a EUA and/or licensure which is critical to address the existing uncertainties, with high urgency to understand homologous and heterologous boosting, both for improved coverage of variants of concern and due to limitations of global vaccine availability. The VIBRI Consortium proposes to carry out a Multi-Centre Phase 2b RCT to evaluate the Safety and Immunogenicity of the Janssen Ad26COVS1 and the Novavax NVX-CoV2373 used as homologous and heterologous boost strategies among HIV positive adolescents and adults with a small control arm of HIV (-) participants. The trial will enroll adolescents and adults aged 12 to 64 years, who have completed a primary series with a homologous vaccine series based on any one platform of a) mRNA (Moderna or Pfizer), b) adenovirus 26 (J&J) or c) inactivated (Sinopharm or Sinovac). These three have been the main vaccine platforms introduced across the three participating countries (Kenya, Democratic Republic of Congo and Rwanda) as of the current protocol. Participants must have completed the primary series at least 3 months prior to enrollment. Given the difference in vaccine rollout between countries, the timing of enrollment within each country is expected to stagger.

This study will be a multi-centre, randomized, double-blind, phase 2b trial to assess the safety, and immunogenicity of Janssen Ad.26COV2.S1 and Novavax NVX-CoV2373 booster vaccines in adults 18-64 years of age and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT)) vaccine in adolescents 12-17 years of age. Adolescent enrollment will be staggered to allow for an initial safety assessment in a sub-set of 300 HIV (+) adults before enrollment. The safety of the booster vaccines will be evaluated by the Data Safety Monitoring Board (DSMB) in the first 300 HIV (+) adult participants 18-64 years through day 28 (Visit 4). Once the DMSB provides their assessment of an acceptable safety in this subset of adult subjects, then adolescents may begin enrollment.

Using a block randomization approach based on primary vaccine platform, approximately equal number of adult participants from each primary platform (mRNA, Adeno26, inactivated) will be enrolled to achieve a total of 1,350 HIV (+) participants (n~ 450/primary platform) and 300 HIV (-) participants (n~ 100/primary platform). Adults will be stratified 2:1 by age (18-44; 45-64) within each primary platform with a goal of 2:1:1 distribution of all adults across Kenya, Democratic Republic of Congo (DRC) and Rwanda. However, adjustments for country level enrollment may be needed to achieve the age strata and the primary vaccine series distribution and study enrollment target.

As adolescents may not have received similar vaccine distribution as adults. Therefore, a minimum number of 150 adolescents across at least one (1) primary platform will be enrolled and a maximum of 300 subjects could be enrolled. The primary vaccine group for the adolescent cohort at this point in the 3 countries is the mRNA Platform, specifically Pfizer vaccine and therefore at least 150 enrolled subjects are possible.

2.2 STUDY RATIONALE

As of Jan 2022, there are over 328 million SARS-CoV-2 case worldwide and over 5.54 million deaths as a result of infection with SARS-CoV-2 (COVID-19). According to WHO Situation report obtained 17 January 2022, Africa has 7 million confirmed cases with over 160, 804 deaths. The COVID-19 pandemic has caused global suffering, mortality, and severe economic pressures.

The FDA and WHO have both recommended that continued evaluation of vaccine effectiveness following issuance of Emergency Use Authorization (EUA) and/or licensure and WHO listing of COVID-19 vaccines. This is critical to address the data gaps that exist despite the rapid successes in vaccine development. WHO SAGE Interim Reports and FDA EUA for COVID-19 vaccines so far evaluated have stated there is limited safety and efficacy data in special populations such as children and adolescents less than 18 years of age, pregnant women, and immunocompromised individuals including People Living With HIV/AIDS (PLWHA) who have been shown to be at higher risk of severe COVID-19 disease. Africa is especially vulnerable in this respect given the high prevalence of HIV/AIDS in countries such as Kenya where the prevalence is more than 20% in certain regions (KENPHIA) 2018). In Kigali, Rwanda the prevalence estimate was 6% (UNAIDS 2017) and in the greater Kinshasa-DRC, prevalence was 11% (Pour M, et al. 2020).

The risk of recurring new waves of COVID-19 cases caused by Variants of Concerns (VOC) exacerbate global public health crisis. A weak immune response to either single or two doses of primary vaccination against SARS-CoV-2 has been observed in immunocompromised population. Emerging data from observational studies consistently show waning immunity to primary vaccination or SARS-CoV-2 mutants, and a decline in vaccine effectiveness against SARS-CoV2 infection and COVID-19 with time since primary vaccinations. These factors have led to consideration of the potential need for, and optimal timing of, booster doses for vaccinated populations. Vaccine inequality, lack of availability of the same vaccine product used for primary vaccinations and unpredictable vaccine supply remain a challenge in LMIC.

Consideration of heterologous COVID-19 vaccine to allow interchangeability (mix and match) use of vaccine products available in LMIC would therefore allow for programmatic flexibility.

The FDA and WHO have both recommended continued evaluation of vaccine effectiveness following issuance of a EUA and/or licensure which is critical to address the existing uncertainties, with high urgency to understand homologous and heterologous boosting, both for improved coverage of variants of concern and due to limitations of global vaccine availability. The VIBRI Consortium proposes to carry out a Multi-Centre Phase 2b RCT to evaluate the Safety and Immunogenicity of the Janssen Ad26COVS1 and the Novavax NVX-CoV2373 used as homologous and heterologous boost strategies among HIV positive adolescents and adults with a small control arm of HIV (-) participants. The trial will enroll adolescents and adults aged 12 to 64 years, who have completed a primary series with a homologous vaccine series based on any one vaccine platform of a) mRNA (Moderna or Pfizer), b) adenovirus 26 (J&J) or c) inactivated (Sinopharm or Sinovac). These three have been the main vaccine platforms introduced across the three participating countries (Kenya, Democratic Republic of Congo and Rwanda) as of the current protocol. Participants must have completed the primary series at least 3 months prior to enrollment. The study has been justified based on the WHO Strategic Advisory Group of Experts (SAGE). Beyond that, the issues of homologous and heterologous vaccinations are known to influence booster vaccine choice. It is therefore important to understand the mix and match aspect of booster vaccination in order to generate data that could be used to inform policy in these countries. In addition, to address expanded access and equitable COVID-19 and disruption in vaccine supplies, it's important for African countries to evaluate different COVID-19 boosting regimens as a strategy to ensure sustainability of its COVID-19 vaccination programs.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The following potential risks will be monitored during the study and are specified below:

2.3.1.1 Risks Related to Vaccination

Several clinical studies of the Janssen COVID-19 vaccine have been conducted in more than 70,000 adult participants worldwide. On 2nd April 2021, Janssen started enrolling adolescents 12-17 years into a new adolescent clinical study. The Novavax COVID-19 vaccine has been evaluated in several clinical studies in adults with more than 50,000 participants taking part.

In general, intramuscular (IM) injection may cause local itching, warmth, pain, tenderness, erythema, swelling, arm discomfort or bruising of the skin at vaccine injection sites. In addition, participants may experience headache, chills, joint pain, muscle pain, tiredness, generally not feeling well, nausea and fever have been seen with these study vaccines. These reactions usually start within 1 to 2 days after the injection and most of the reactions get better within 1 to 3 days.

More detailed relevant information about potential risks are provided in the Investigator's Brochures for the Janssen Ad26COVS1 and Novavax NVX-CoV2373 vaccines.

2.3.1.2 Risks of accidental disclosure of Personal Health Information (PHI)

In order to ensure that all information collected on study volunteers is kept confidential, the following safeguards will be applied: Access to study files and personal information will be limited to study personnel, ethics committees, regulatory authorities, the sponsor and sponsor representatives. Study information will be kept in locked rooms at the site when not in use. All information or samples that leave the study sites will be labeled with a unique study identification number and have no personal identifying information (PII). Any link between individual study identification number and an individual's PII (e.g., an individual's study file and associated documents) will be maintained at the study sites in accordance with site SOPs to maintain each individual's confidentiality.

There may be additional risks associated with disclosure of participants' COVID-19 and HIV status as well as disclosure of any abnormal lab tests found during screening, and careful measures will be taken to ensure confidentiality is maintained. Participants who are tested will undergo pre- and post-test counseling in accordance with respective National Guidelines. Standard pre-testing and post-testing counseling and linking to care will be followed. In the event that a participant is diagnosed with SARS-CoV-2 infection, the testing laboratory will report the result to the respective National Ministry of Health as per the guidelines on COVID-19. To the greatest extent possible, abnormal tests will be communicated to participants and screen failures in simplified language and referrals made to health care provider as appropriate.

2.3.1.3 Risk of Injury as a result of participation in the study

If a participant is injured as a direct result of participation in this study, the medical care will be provided by the study team at the respective study sites or will be referred appropriately to a hospital or health care provider, and the study will pay for the expenses. The participant will be compensated using the clinical trial insurance obtained for this trial.

2.3.1.4. Risk of phlebotomy and mucosal secretion sampling

Venipuncture is a routine clinical procedure the medical community commonly uses to obtain blood samples. Immediate complications may be slight pain during the entry of the needle into the skin, very rarely possible dizziness, and syncope. Additionally, a hematoma may result from the venipuncture, but this has minimal risk. Infection of the skin/soft tissue at the puncture site, vein, or blood stream can all occur, though are very rare with venous blood draws. Late complications might include thrombosis of the vein due to trauma or infection. These complications are extremely rare. Participant monitoring, aseptic technique, including sterile disposable blood collection apparatus and adherence to standard medical precautions reduce any risk to a minimum. A credentialed phlebotomist or member of the clinical team experienced in venipuncture techniques will perform all venipunctures. The amount of blood to be taken

for sampling will not be harmful to the participant's health. When appropriate for adolescents, a numbing cream or spray may be used to reduce discomfort.

Sampling of mucosal secretions is a standard procedure and during COVID has been successfully completed without medical supervision. Nasosorption™ FX·I is a nasal sampling device which uses a synthetic absorptive matrix (SAM™) swab to gently absorb mucosal lining fluid from the mucosa within the nose. It is designed for targeted sampling with minimal patient discomfort. The device will be shown to participants and the procedure explained before sampling is performed. Inspection of the nasal cavity to confirm no obstruction, ulcers or masses are present. Sampling may cause sneezing, rarely irritation and very rarely nose bleeds.

2.3.1.5 Unknown Risks

There may be other risks that are not known. If any significant new risks are identified, the Principal Investigator and participants (parents/guardians) will be informed**.**

2.3.2 KNOWN POTENTIAL BENEFITS

All volunteers for this study will receive the following benefits for their participation:

- All volunteers will undergo a medical examination at screening free of charge. All volunteers, whether accepted for enrolment into the trial or not will benefit from this free health check-up. The results of all tests will be communicated to all volunteers. Where illnesses are newly-diagnosed, a referral to an appropriate health provider will be made for the volunteer.
- For the duration of their participation in the trial, study participants will receive health care for acute conditions. In case of chronic conditions, participant will be referred to appropriate health providers.
- All volunteers in the study will receive a SARS-CoV-2 vaccine booster that have been shown to protect against severe SARS-CoV-2.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this clinical study is considered acceptable for the following reasons:

- To date, safety data from the COVID-19 vaccine studies have shown a favorable safety profile. There are ongoing trials and long-term safety follow up after issuance of EUA that will add to the evidence of safety of the study vaccines during the course of the study. Any new safety information on either vaccine used in the study will be provided to all participants in appropriate level of understanding to ensure informed consent remains in place.
- The study provides for pausing rules based predefine safety outcomes that will result in pausing of further vaccination if predefined conditions occur, preventing exposure of new participants to study intervention until a DSMB evaluates all safety data.

- Enrollment of participants will be determined by the study investigators where only participants who meet eligibility Criteria will be considered for enrollment.
- Safety measures have been included in the protocol to minimize the potential risk to participants, including the following:
    a. Post vaccination observation to monitor reactogenicity at the study site for 30-60 minutes
    b. Clinical (physical examinations +/- vital sign measurements) will be performed during study visits based on medical need.
    c. As part of safety follow up, the study team will assess adverse events (Solicited Adverse Events, Unsolicited Adverse Events, Treatment Emergent Adverse Events (TEAE), Serious Adverse Events (SAE), and AESI) through various timeframes.
- Monitoring for breakthrough COVID-19 cases (along with symptoms and severity scoring) will occur throughout the duration of the study.
- During the study, participants will be monitored for acute illnesses and managed in accordance with country specific standard of care.

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVES

3.1.1. PRIMARY SAFETY OBJECTIVES

Objectives	Endpoints
To evaluate reactogenicity (solicited adverse events (AEs) Ad26.COV2S1 and NVX-CoV2373 for adults or for adults or NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccine for adolescents following boosting.	Occurrence of solicited AEs (local and systemic) reactogenicity events through 7 days following boosting vaccination. Analysis to include by HIV status, age group, booster treatment group, homologous and heterologous vaccination series (primary platform + boosted vaccine).
To evaluate Serious Adverse Events related to vaccination of Ad26.COV2S1 or NVX-CoV2373 for adults or NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccine for adolescents during the entire study.	Incidence of vaccine related Serious Adverse Events (SAEs) throughout the study period. Analysis to include by HIV status, age group, booster treatment group, homologous and heterologous vaccination series (primary platform + boosted vaccine).

3.1.2. PRIMARY IMMUNOGENICITY OBJECTIVE

Objective	Endpoints
To evaluate the immunogenicity of Ad26.COV2S1 and NVX-CoV2373 vaccines for adults or NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccine for adolescents at day 28	1. SARS-CoV-2 neutralization: SARS-CoV-2 neutralizing titers in serum measured by a virus neutralization assay (VNA) using pseudovirion expressing S protein (standardized to 50% neutralization with 95% CI). 2. Serum IgG antibodies to SARS-CoV-2 rS protein measured by enzyme-linked immunosorbent assay (ELISA) using geometric mean titers (GMT with 95% CI). 3. Geometric mean fold ratio over baseline (IgG and VNA). Analysis to include by HIV status, age group and booster treatment group (Ad26.COV2S1 or NVX-CoV2373) or mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccine

3.2 SECONDARY OBJECTIVES

3.2.1. SECONDARY SAFETY OBJECTIVES

Objectives	Endpoints
To evaluate all unsolicited AEs post-vaccination through 28 days and Treatment Emergent Adverse Events (TEAEs) through day 85 in all participants.	Incidence of unsolicited AEs and TEAEs by MedDRA coding (high ordered term and preferred term), severity and relatedness. Analysis to include by HIV status, age group, booster treatment group, homologous and heterologous vaccination series (primary platform + boosted vaccine).

To evaluate safety in terms of Adverse Events of Special Interest (AESIs) following vaccination, for all participants through end of study.	Incidence of AESIs for all participants following vaccination through the EOS. Analysis to include by HIV status, age group, booster treatment group, and primary vaccination platform/series. AESI will be assessed as Potential Immune Mediated Medical Conditions (PIMMC) or events deemed of special interest by COVID-19 disease.
To describe Serious Adverse Events (SAEs) through end of study in all participants.	Analysis to include by HIV status, age group, booster treatment group, and primary vaccination platform/series.

3.2.2. SECONDARY IMMUNOGENICITY OBJECTIVES

Objectives	Endpoints
To compare the immunogenicity of heterologous boost in participants at Day 28 (IgG ELISA and neutralization)	Means and 95% CI for VNA, GMT, geometric mean fold rise (GMFR) from baseline to Day 28. Analysis to include by HIV status, age group, treatment group, adolescents boosted at ≥5-12 or >12 months and primary vaccination series/platform.
To compare the durability of response through end of study (IgG ELISA and neutralization)	Mean and 95% CI for VNA, GMT, geometric mean fold rise (GMFR) at each study visit. Analysis to include by HIV status, age group, treatment group, adolescents boosted at ≥5-12 or >12 months and primary vaccination series/platform.
To evaluate mucosal immunogenicity of homologous and heterologous boost in participants at Day 28 (S-IgA ELISA).	Mucosal secretory (S-IgA) to SARS-CoV-2 rS protein measured by enzyme-linked immunosorbent assay (ELISA) using geometric mean titers (GMT) and GMFR at Day 28. Analysis to include by HIV status, age group, treatment group, and primary vaccination series/platform.

3.3 EXPLORATORY OBJECTIVES

Objectives	Endpoints
To evaluate the occurrence SARS-CoV-2 infection and level of severity in participants	Incidence of rapid antigen and virologically confirmed SARS-CoV-2 starting at Day 28 through EOS in all participants, by subject reported symptomatology, duration and severity. Classification as asymptomatic, mild, moderate or severe along with analysis of symptomatology (type/duration) and time to symptom resolution and time to negative rapid Ag test will be derived. Analysis to include HIV status, age group, booster treatment group, and vaccination platform/series.
To evaluate the occurrence SARS-CoV-2 infection variants of concern in all participants with moderate to severe disease following booster vaccination.	Incidence of virologically confirmed SARS-CoV-2 variants of concern (e.g., B.1.351, B.1.1.7, B.1.617, B.1.1.529, or others to be identified as the pandemic evolves)-COVID-19, starting at Day 28 through EOS in participants who develop

	moderate or severe COVID-19 disease. Analysis to include HIV status, age group, booster treatment group, vaccination platform/series and SARS-CoV-2 severity grade.
To evaluate the Cell Mediated Immune response of Ad26.COV2S1 and NVX-CoV2373 vaccines in adults HIV (+) and HIV (-) participants	SARS-CoV-2 Cell Mediated Immunity in Peripheral Mononuclear Cells (PBMCs) as measured by ELISPOT at baseline and on Day 7 following boost. Analysis to include boost treatment group and primary vaccination platform/series.
To identify a threshold of immune protection for HIV (+) and HIV (-) participants to prevent SARS-CoV-2 infection following booster vaccination.	Analysis of breakthrough cases with GMT and VNA levels to determine a potential threshold of protection (through EOS).
To assess if changes in control of HIV infection (by viral loads and CD4 counts) has an effect on immune responses or breakthrough SARS-CoV-2 infection rates/severity during the trial	Assessment of changes in HIV viral loads and CD4 counts during long term immune durability within HIV subjects (by booster and by primary vaccination platform).

4 STUDY DESIGN

4.1 STUDY SETTING

4.1.1 VICTORIA BIOMEDICAL RESEARCH INSTITUTE, KENYA

Victoria Biomedical Research Institute (VIBRI) is a non-profit organization based in Kenya providing pharmaceutical, academic research, and non-profit organizations with a network of clinical sites and expertise focusing on accelerating transformative therapeutics, vaccines, and devices research for major global health diseases in Africa. VIBRI is located at the Kisumu County Referral Hospital in Kisumu County, western Kenya (*see Figure 1 below*).

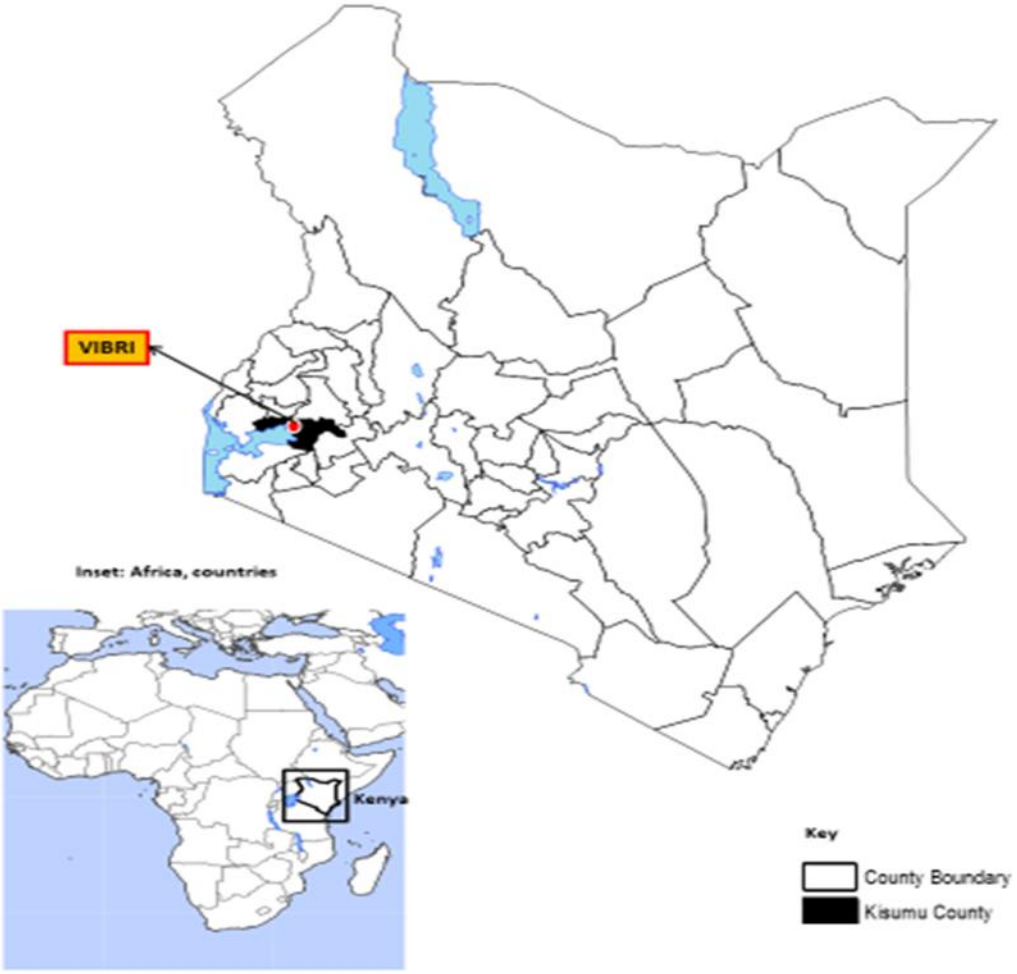

Figure 1: Map of Kenya showing Kisumu County.

VIBRI was established to conduct biomedical research including clinical trials, bioequivalence studies, basic science research studies, epidemiology and population health studies, implementation science studies, build a strong foundation in data science, conduct training and capacity building on clinical research in Kenya. VIBRI has experienced and accomplished clinical research scientists who have designed

and conducted GCP compliant phase 1b to phase IV paediatric and adult clinical trials on vaccines and drugs for different indications including malaria, HIV, tuberculosis, diarrhea, sickle cell disease, ebola, pneumonia, polio among many others. The VIBRI Clinical Trials site will conduct trial activities out of the Kisumu County Referral Hospital and surrounding health facilities. The staff and infrastructure can serve several satellite sites for reaching high-risk populations from Kisumu City. All members of the clinical trial team are trained in GCP and Human Participants Protection. The research team has a close affiliation with the Kenya Ministry of Health at the county and national levels and with the personnel working in the Ministry of Health facilities within the study area. Trained VIBRI staff and Ministry of Health Community Health Workers will assist with study activities conducted in the field and in satellite facilities.

Kisumu County is one of 47 counties in the Republic of Kenya. Its headquarters is Kisumu City which is the third largest city in Kenya. It has a population of 1,155,574 (Kenya National Bureau of Statistics, 2019). The land area of Kisumu County totals 2085.9 km^2. The county has a shoreline on Lake Victoria, occupying northern, western and a part of the southern shores of the Winam Gulf. The city of Kisumu has historically functioned as a major center of Western Kenya commerce. Health in Kisumu County is provided by several institutions that are either private or government funded. There is one teaching and referral hospital, 5 County referral hospitals, 14 sub-county hospitals, 74 dispensaries and 18 health centres in the county.

4.1.2 RINDA UBUZIMA/UNIVERSITY OF RWANDA, RWANDA

In Rwanda, the study will be carried out by Rinda Ubuzima, a Non-Governmental Organization which is housed within the University of Rwanda. Rinda Ubuzima is the continuation of the former Project Ubuzima; an International Non-Governmental Organization founded in 2004 in Amsterdam by members of Management Team of the International Antiviral Therapy Evaluation Center (IATEC). Rinda Ubuzima has more than 15 years of experience in the field of clinical trials marked by intensive capacity building and acquisition of clinic and laboratory equipment. Rinda Ubuzima is operating Clinical Trials and Laboratory Research in Kigali and has successfully implemented various studies, focusing on HIV, Reproductive Health and Malaria. In addition to the clinical trial activities, Rinda Ubuzima has extended its area of expertise to include conducting and implementing community engagement and outreach activities as well as social science.

To achieve its mission, Rinda Ubuzima has fixed itself the following objectives:

- To collaborate with researchers from all over the world (Africa, Europe, Asia, North and South America) to support medical research in Rwanda.
- To conduct/implement the clinical trials and other studies to move medicine forward, through medical and global health research.
- To contribute to capacity building in clinical trials and social sciences activities.
- To conduct health promotion activities through community engagement and outreach, respecting the GPP (Good Participatory Practice).
- To closely collaborate with University of Rwanda in implementing public health issues.
- To closely collaborate with Rwanda Ministry of Health in clinical trials issues.

Rwanda is a small mountainous and land locked country of 26,338 square kilometers and lying just south of the equator with an average elevation of 1,700 meters. Approximately 76 percent of the land is fit for cultivation. Rwanda's population is growing rapidly with implication on the demographic situation. The most recent population census conducted in 2012 estimated the population to be around 10.5 million people and the population density is the highest in Sub-Saharan Africa (416 inhabitants per square kilometer). The population is essentially young, with 52 percent of all Rwandans under the age of 20. In terms of gender, the 2012 census shows females to be in the majority (52 percent) of the population (NISR, 2012). The illiteracy rate declined from 34 percent to 15.5 percent among women and from 24 percent to 10.3 percent among men between 2005 and 2010 (DHS 2005 and 2010).

In the last 20 years, the Government of Rwanda (GoR) successfully designed and implemented a broad set of policies and programs of economic reform and decentralization to enhance local capacity. Rwanda is committed to the international and regional agreements for which it is a signatory such as the SDGs. Efforts have been made to develop the service sector and stimulate investment in the industrial sector; however, the Rwandan economy remains dominated by agriculture. The health sector has a crucial role to play in the achievement of the national mid-term Economic Development and Poverty Reduction Strategy (EDPRS 2) goal of 11.5% economic growth rate. Continuous progress in the coverage and quality of promotive, preventive, curative and rehabilitative health interventions and in the health seeking behavior of the population ensure improvements in the health status and productivity of the Rwandan population. Availability of high-quality health services, as an important element of the service sector, contributes to the generation of collective wealth and is crucial to attracting investors and tourists.

4.1.3 UNIVERSITY OF KINSHASA (UNIKIN), THE DEMOCRATIC REPUBLIC OF CONGO (DRC)

In the DRC, the study will be carried out by the Department of Tropical Medicine, Faculty of Medicine at the University of Kinshasa (UNIKIN). This department has three missions: training of doctors in the field of infectious and parasitic diseases, research and services in the community (health care). The department of tropical medicine collaborates with several disease control programs of the Ministry of Health and the National Biomedical Research Institute. As such, these members participate as experts in several health projects. Department staff play an important role in changing health policies and generating evidence for the Ministry of Health. The Ministry of Health through the General Secretary of Health recommends every two years about twenty doctors for specialization training in the field of tropical medicine. The members of the Department are skilled in design and implementation of studies in the remote areas in the DRC, where the conditions are challenging. The Department of Tropical Medicine has a clinical research unit which has conducted, with the support of some international organizations (DGD, EDCTP, FIND, VLIR, IMI, etc.) several research studies on malaria, human African trypanosomiasis, schistosomiasis, cervical cancer, Ebola viral disease, etc. The clinical research unit was strengthened by a long-lasting and fruitful collaboration with the Global Health Institute of the University of Antwerp.

The Democratic Republic of Congo (DRC) is the largest country in Sub-Saharan Africa. After more than three decades, the Democratic Republic of the Congo (DRC) adopted a Constitution that enshrined a highly decentralized state. Parliaments and governments were established at the provincial level and at the

national level. These political changes came at a time of considerable progress in terms of economic growth and macroeconomic stability. Between 2008 and 2012, gross domestic product (GDP) grew at an average rate of 6.1% per year. After the global economic crisis of 2009, the DRC achieved growth rates that were consistently higher than the average for sub-Saharan Africa. Investments in the extractive industries and the effects of dynamic growth in agriculture, construction and trade resulted in economic growth of 7.2% in 2010 and again in 2012. Structural reforms that enabled the country to attract more foreign capital contributed to a new dynamism in the Congolese economy. The cancellation of 90% of the external debt in 2010 as part of the Heavily Indebted Poor Countries initiative expanded fiscal space and gave the State more means to carry out its policy of reconstruction.

The health system of the DRC is organized in three levels. At the implementation level there are 516 health districts, where a district team manages a network of health centres and a district hospital. Districts typically cover a population of 100 000 to 200 000. The intermediate level, responsible for technical and logistic support, is managed by provincial health departments, the number of which has recently increased from 11 to 26. The central level has a normative role. The process of revitalizing the health sector in the DRC started in 2005 with the adoption of the Health System Strengthening Strategy (HSSS). The strategy was developed by key national actors following extensive discussions and analyses of the history and political economy of the health sector and the health status of the population. It provides a framework for reforms to overcome inefficiencies in the sector and the marginalization of national policy-making in a context of dependency on external aid. This study will be conducted in Kinshasa, the capital city. Depending on the recruitment speed, the UNIKIN team may extend recruitment in Haut-Katanga, Nord-Kivu and Tshuapa provinces.

4.2 STUDY DESIGN

This will be a Multi-Centre, Multi-Stage, Randomized, Double Blind, Phase 2b Trial to Evaluate the Safety and Immunogenicity of Janssen Ad26COVS1 and Novavax NVX-CoV2373 COVID-19 vaccines for adults or NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents administered as homologous and heterologous Boost Regimens in Adolescents (12-17 years) with HIV and in Adults (18-64 Years) with/without HIV infection in 3 African Countries (Kenya, Democratic Republic of Congo and Rwanda). Adolescent enrollment will be staggered to allow for an initial safety assessment in a subset of the first 300 HIV (+) adults before enrollment. The safety of the booster vaccines will be evaluated by the Data Safety Monitoring Board (DSMB) in the first 300 HIV (+) adult participants 18-64 years through day 28 (Visit 4). Once the DMSB provides their assessment of an acceptable safety profile in those adult subjects, then adolescents may begin enrollment. The overall study design is depicted in Table 2.

Table 2: Study Design-Homologous and Heterologous Prime-Boost Vaccination Adult Groups

Vaccine Platform for Primary Series	HIV (+) adults (age 18-64)	HIV (-) Adults (age 18-64)	Booster vaccination (5-7 months) 1:1*
mRNA (Moderna mRNA-1273 or Pfizer/BNT)	450	100	Janssen Ad26COVS1
			Novavax NVX-CoV2373
Adenovector 26 (Janssen Ad26COVS1)	450	100	Janssen Ad26COVS1
			Novavax NVX-CoV2373
Inactivated whole virus (Sinopharm-BIBP or Sinovac)	450	100	Janssen Ad26COVS1
			Novavax NVX-CoV2373
Total	**1,350**	**300**	**Maximum 1,650**

Table 3: Study Design-Homologous and Heterologous Prime-Boost Vaccination Adolescent Groups

Vaccine Platform for Primary Series	HIV (+) adolescents (age 12-17)	Booster vaccination (≥5 months) 1:1
mRNA (Moderna mRNA-1273 or Pfizer/BNT)	150	Novavax NVX-CoV2373
	150	Moderna mRNA-1273 or Pfizer/BNT**
Total	**Maximum 300**	**Maximum 300**

*Booster vaccination for adolescents will be ≥5 months after the last primary vaccination series consistent with US CDC and FDA recommendations.

** Monovalent or bivalent vaccines depending on MOH availability and supply.

Using a block randomization approach based on primary vaccine platform, approximately equal number of participants from each primary platform (mRNA, Adeno26, inactivated) will be enrolled. Among HIV (+) participants, randomization will occur across 3 primary vaccine platforms with approximately 450 adults/platform (expected 2:1 distribution of ages 18-44:45-64). In addition, a group of 300 HIV (-) adult participants (aged 18-64) will be enrolled who have received a homologous primary series from one of the three platforms (~100/primary platform). All adult participants will be randomized 1:1 within their primary vaccine platform to receive a single dose of either Janssen Ad26COVS1 vaccine or Novavax NVX-CoV2373 COVID-19 vaccine between 5 and 7 months from completion of their primary series. All adolescent participants will be randomized 1:1 to receive either Novavax NVX-CoV2373 or mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines ≥5 months after the primary series as shown in (Table 3). The ≥5 months adolescent booster vaccination interval is consistent with new guidance from the US CDC and FDA (16, 17, 18) and is more reflective of real-world settings implementation of country MOH COVID-19 vaccination programs. Due to the uncertainty of vaccine supply and to allow for adequate capture of participants, the pre- booster vaccination enrollment period will vary anywhere from -85 days to 0 days at the time of boost. Adults will be stratified 2:1 by age (18-44; 45-64) within each primary platform with

a goal of 2:1:1 distribution of adults from Kenya, DRC and Rwanda. However, adjustments for country level enrollment may be needed to achieve the age strata and the primary vaccine series distribution and study enrollment target.

As adolescents may not have received similar vaccine distribution as adults, a maximum of 300 across the primary platforms and a minimum of 150 adolescents across one (1) primary platform may be enrolled. The primary vaccine group for the adolescent cohort at this point in the 3 countries is the mRNA Platform, specifically Pfizer/BNT vaccine.

Due to the uncertainty of vaccine supply and to allow for adequate capture of participants, the pre-booster vaccination enrollment period may vary anywhere from -85 days to 0 days from the time of boost (Day 0) with the adolescent booster delivered between 5- and 12-months following completion of the adolescent primary series.

There will be 3 interim analysis time points by primary vaccine platform: a) 28 days following booster vaccination of adults/adolescent (safety and immunogenicity); b) 6 months after adult/adolescent boost vaccinations; c) 12 months after boost vaccination for all subjects (safety, immunogenicity and SARS-CoV-2 breakthrough infections). The interim analyses will be at the treatment level only and blinding will remain at the individual level, site level and for all operational teams and sponsor. The final database lock and analysis will occur after adult participants have completed the long term follow up (15-18 months) and 12 months for adolescent participants. Both Sponsor and DSMB will have interim analyses available for decision making.

As immunologic durability in HIV (+) participants is relatively unknown, should the loss of immunity be observed at 6 months (significant reduction in GMT among HIV (+) participants compared to HIV (-) participants over the same time period), or if efficacy of SARS-CoV-2 vaccination appears to demonstrate waning after 12 months (accrual of breakthrough moderate and severe cases by review of DSMB), or new data emerges that vaccine boosting is not sustained over time then participants may be re-boosted with the same vaccine used for the initial boost. Alternatively, the study may be terminated early to allow re-boosting to occur under national guidelines with appropriate vaccines indicated. This determination will be made by the DSMB based on ongoing reviews following interim analyses with quarterly meetings after all participants have enrolled to provide adequate oversight of safety and provide guidance on needs to implement an alternative boosting vaccination strategy.

At the time of enrollment, participants will provide a blood sample for immunity. If enrollment occurs greater than 30 days prior to randomization, then participants will provide an additional sample on the day of randomization/booster vaccination (prior to receiving the vaccine). The serum sample provided at -30 to 0 days relative to the booster vaccination will be considered the baseline sample. Participants will be followed for reactogenicity through 7 days following booster vaccine and for unsolicited Adverse Events through 28 days following booster vaccine. Participants will continue to be followed for any Treatment Emergent Adverse Events (TEAE) through day 85, AESI and any SAE or COVID disease occurrence through EOS. Serum samples for immunogenicity testing (IgG ELISA and neutralization) will be taken at time of enrollment (unless as noted above), days -30 to 0 Days (relative to vaccination) and

28D, 85D, 6M, 12M and 15-18M following booster vaccination. All adults will contribute 2 samples for mucosal immunity taken with a leukosorb nasal swabs at baseline (Visit 2) and Day 28 (Visit 4) following booster vaccination.

Samples for Cellular Mediated Immune (CMI) response will be taken in a subset of adult participants, located at the Kisumu site in Kenya. No more than 60 HIV (+) and 30 HIV (-) participants within each primary vaccine platform will contribute to CMI testing based on subjects agreeing at the time of consent (opting in). As it may not be possible to achieve equal distribution across primary vaccination platforms or consenting by subjects, this is the maximum planned and stratification will be performed for balance between the booster vaccine arms within the platforms. Samples will be taken at baseline (V2) and again at Day 7 (V3) following booster vaccination.

SARS-CoV-2 symptom and exposure inquiries will be performed every month by field staff or via electronic media as well as at each visit. In addition, participants are encouraged notify staff if symptoms consistent with SARS-CoV-2 are evident or known exposure has occurred and they will be organized to be seen in an unscheduled visit. Participants will provide a nasal sample test using a Rapid Antigen Test or PCR. If a rapid Ag test is (+), then this will be confirmed by a nasopharyngeal RT-PCR test. Any positive Rapid Antigen test will result in daily self-monitoring of symptoms over a 10-day period using a diary (self-evaluation symptom scoring tool) with each confirmed case receiving a final classification of asymptomatic, mildly symptomatic, moderately symptomatic or severely symptomatic by modified WHO classifications (Table 4). In addition, participants will return for a SARS-COV-2 antigen test after 10 days. If the rapid antigen test is positive, then subjects will again provide a nasopharyngeal sample for RT-PCR. Subjects will continue to return to the clinic every 10 days for retesting until negative. In addition, subjects will continue with daily monitoring of symptoms with a self-directed diary until symptom free. Anytime exposure or COVID-19 symptoms occur this testing algorithm will be followed. A reinfection is classified once at least one test following primary infection has been negative. All subjects with a positive RT-PCR test result depending on the CT value will be considered for possible sequencing to determine SARS-CoV-2 variants of concern (VoC) . Length of time of positivity will be reported descriptively given the resample timing. Highest level of SARS-CoV-2 severity will be applied for each participant.

Table 4: WHO COVID-19 Case Definitions for Severity

COVID-19 Severity	Definitions
Virologically Confirmed SARS-CoV-2	All SARS-COV-2 asymptomatic and symptomatic cases confirmed by Rapid Ag testing beginning 28 days following boost until end of study.
Asymptomatic and virologically confirmed	Positive by Rapid Ag test but without sufficient symptoms at presentation or during symptom monitoring phase to be classified by symptomatic.
Mildly Symptomatic and Virologically confirmed	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) OR • New onset cough OR • ≥ 2 COVID-19 respiratory/non-respiratory symptoms

	AND • Does not meet criteria for moderate or severe
Moderately Symptomatic and Virologically confirmed	≥ 1 of: • Fever (defined by subjective or objective measure, regardless of use of anti-pyretic medications) + any 2 COVID-19 symptoms for ≥ 3 days OR • High fever (≥ 38.4°C) for ≥ 3 days (need not be contiguous days) without other cause documented OR • Any evidence of significant LRTI: − Shortness of breath (or breathlessness or difficulty breathing) with or without exertion (greater than baseline) − Tachypnea: >20 breaths per minute at rest − SpO2: < 95% on room air − Abnormal chest x-ray or chest CT consistent with pneumonia or LRTI − Adventitious sounds on lung auscultation (e.g., crackles/rales, wheeze, rhonchi, pleural rub, stridor) AND • Does not meet criteria for severe disease
Severely Symptomatic and Virologically confirmed	≥ 1 of: • Tachypnea: ≥ 30 breaths per minute at rest OR • Resting heart rate ≥ 125 beats per minute OR • SpO2: ≤ 93% on room air or PAO2/FiO2 < 300 OR • High flow oxygen therapy or NIV/NIPPV (e.g., CPAP or BiPAP) OR • Requirement for vasopressors, systemic high dose corticosteroids, hemodialysis or extracorporeal blood circuitry support for renal/hepatic malfunction OR • One or more major organ system dysfunction or failure (e.g., cardiac/circulatory, pulmonary, renal, hepatic, and/or neurological, to be defined by diagnostic testing/clinical syndrome/interventions), including any of the following: − ARDS − Acute renal failure − Acute hepatic failure − Acute right or left hear failure − Septic or cardiogenic shock (with shock defined as SBP < 90 mmHg OR DBP < 60 mm Hg) − Acute stroke (ischemic or hemorrhagic) − Acute thrombotic event: AMI, DVT, PE − Other organ dysfunction as outlined by Safety Platform for Emergency vACcines (SPEAC)for Covid-19 complications
Abbreviations: AMI = acute myocardial infarction; ARDS = acute respiratory distress syndrome; BiPAP = bi-level positive airway pressure; COVID-19 = coronavirus disease 2019; CPAP = continuous positive air pressure; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep vein thrombosis; FiO2 = fraction of inspired oxygen; ICU = intensive care unit; LRTI = lower respiratory tract infection; NIV = non-invasive ventilation; NIPPV = non-invasive positive pressure ventilation; PAO2 = partial pressure of oxygen in the alveolus; PE = pulmonary embolism; SBP = systolic blood pressure; SpO2 = oxygen saturation	

4.3 SAMPLE SIZE

The sample size is estimated to be adequate based on boosting data available for both vaccines if a similar response is observed in HIV (-) participants. The HIV (-) control has been incorporated into the study design to allow for monitoring of both immunity and safety in an immunocompetent population to observe for similar magnitude in responses over time (descriptive). The sample size is based on calculations to achieve testing at Day 28 of significance over baseline and comparison of assessments between the 2 vaccine treatment arms in HIV (+) adults at the level of primary vaccine platform.

We compute the booster vaccine trial sample size based on the following primary objectives:

1. To evaluate reactogenicity (solicited adverse events (AEs) Ad26.COV2S1 and NVX-CoV2373 for adults or NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents following boosting.
2. To evaluate Serious Adverse events related to vaccination of Ad26.COV2S1 vs NVX-CoV2373 for adults or NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents during the entire study.
3. To evaluate the immunogenicity of Ad26.COV2S1 and NVX-CoV2373 vaccines for adults or NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents at day 28

As the study seeks to compare reactogenicity and immunogenicity outcomes between HIV+ and HIV- participants as well as between the two vaccine treatment arms (Ad26.COV2S1 vs NVX-CoV2373 for adults and NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents, we calculate the sample size under the following scenarios.

Scenario 1: Evaluating sample size that would detect a difference in (Serious) Adverse Events (AEs) and mean IgG between HIV+ and HIV- participants.

In evaluating significance of solicited and serious adverse events in HIV+ participants, analysis will compare the incidence in HIV+ participants with that observed in HIV- participants. Under this scenario, the expected ratio of HIV+ to HIV- participants is 4.5:1. Therefore for sample size computation, we use the formula in Wittes (2002) which takes into account the imbalance of participants between groups, i.e.:

$$n_{HIV-} = \left(\frac{k+1}{k}\right) \times \left(\frac{\bar{p} \times (1-\bar{p}) \times \left(z_{\beta} - z_{1-\frac{\alpha}{2}}\right)^2}{(p_1 - p_2)^2} \right) \quad (1)$$

Where:

n_{HIV-} = sample size for HIV- participants (smaller group)

k = ratio of sample size in HIV+ to HIV- groups

$p_1 - p_2$ = clinical difference in proportions of AEs (p_1 and p_2 are proportions of AEs in HIV+ and HIV- participants.

z_{β} = corresponds to a power of either 80% or 90%

$z_{1-\alpha/2}$ = corresponds to two-tailed significance level

NOTE: In evaluating sample size that would be sufficient to answer objective 3, $\bar{p} \times (1 - \bar{p})$ is replaced by the variance of the expected mean difference in the two groups, and $p_1 - p_2$ is replaced by the difference in two group means.

We examined the literature to determine the expected proportion of adverse events in HIV+ population. A recent meta-analysis by McDonald (2021) evaluated the difference in AEs between vaccinated individuals and various control groups. The authors found the percentage of solicited adverse events to be 60% and grade 3 (equivalent to serious) AEs to be up to 11% in healthy participants[1]. In addition, the mean logarithm of IgG in each study was found to at least ~ 1000 in equivalent vaccine arms. We therefore adopt a conservative approach, in which we assume that the expected percentage of (i) adverse events would be 60%, (ii) serious adverse events would be 10%, and (iii) the expected mean logarithm of IgG would be at least 1000 in HIV+ participants. We apply these estimates to the defined sample size formula for 80% and 90% power, while varying the detectable difference for the three primary objectives respectively. The findings are presented in **Figure 2**. At a power of 80% and 5% significance level:

- Under objective 1, a sample size of 1980 would be sufficient to detect a risk ratio of 1.20 in solicited AEs in HIV+ participants (compared to HIV- participants).
- Under objective 2, a sample size of 1958 would be sufficient to detect a risk ratio of 1.80 in serious AEs in HIV+ participants (compared to HIV- participants).
- Under objective 3, a sample size of 1980 would be sufficient to detect a mean difference of 80 in logarithm of IgG in HIV+ participants (compared to HIV- participants).

[1]Another study conducted by Wu 2021 found AEs to be about 10% in vaccinated HIV+ participants.

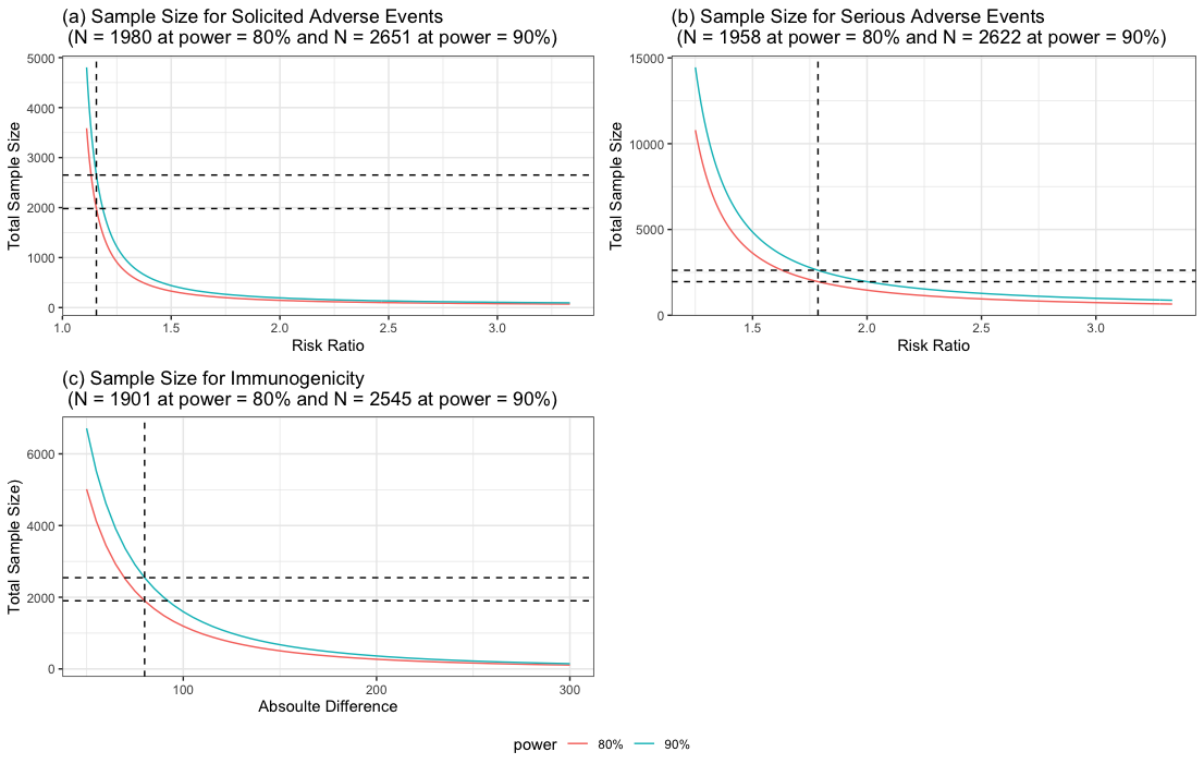

Figure 2: Sample sizes for determining differences in reactogenicity and immunogenicity outcomes between HIV+ and HIV- participants.

Feasible assumptions to support an approximate sample size of 1950:

- Expected incidence of solicited and serious adverse events (AEs) in HIV+ would be approximately 60% and 10% respectively.
- Expected mean logarithm of IgG would be at least 1000 (with a standard deviation of 500).
- Expected detectable risk ratio in solicited and serious AEs in HIV+ participants (versus HIV- participants) would be about 1.2 and 1.8 respectively.
- We expect little to no variation in AEs across the sites, hence no need to adjust the sample size by a design effect.

Scenario 2: Comparison of Ad26COVS1 (mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines **and NVX-CoV2373 vaccine treatment arms in HIV+ participants**

As the analysis will compare the two vaccine treatment arms (Ad26COVS1 and NVX-CoV2373) in adults, and NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents, we evaluate the detectable risk ratios that would be considered plausible. We applied the same formula as scenario 1, and to achieve a ratio of 1:1 participant distribution between the two arms we set k = 1. We also adopt a conservative approach, in which we assume that the expected percentage of (i) adverse events would be 60%, (ii) serious adverse events would be 10%, and (iii) the expected mean logarithm of IgG would be at least 1000 in participants who would be allocated NVX-CoV2373 booster vaccine. We apply these estimates to the defined sample size formula for 80% and 90% power, while varying the detectable

difference for the three primary objectives respectively. The findings are presented in **Figure 3**. At a power of 80% and 5% significance level:

- Under objective 1, a sample size of 1938 would be sufficient to detect a risk ratio of 1.12 in solicited AEs in HIV+ participants (compared to HIV- participants).
- Under objective 2, a sample size of 1938 would be sufficient to detect a risk ratio of 1.53 in serious AEs in HIV+ participants (compared to HIV- participants).
- Under objective 3, a sample size of 2052 would be sufficient to detect a mean difference of 60 in logarithm of IgG in HIV+ participants (compared to HIV- participants).

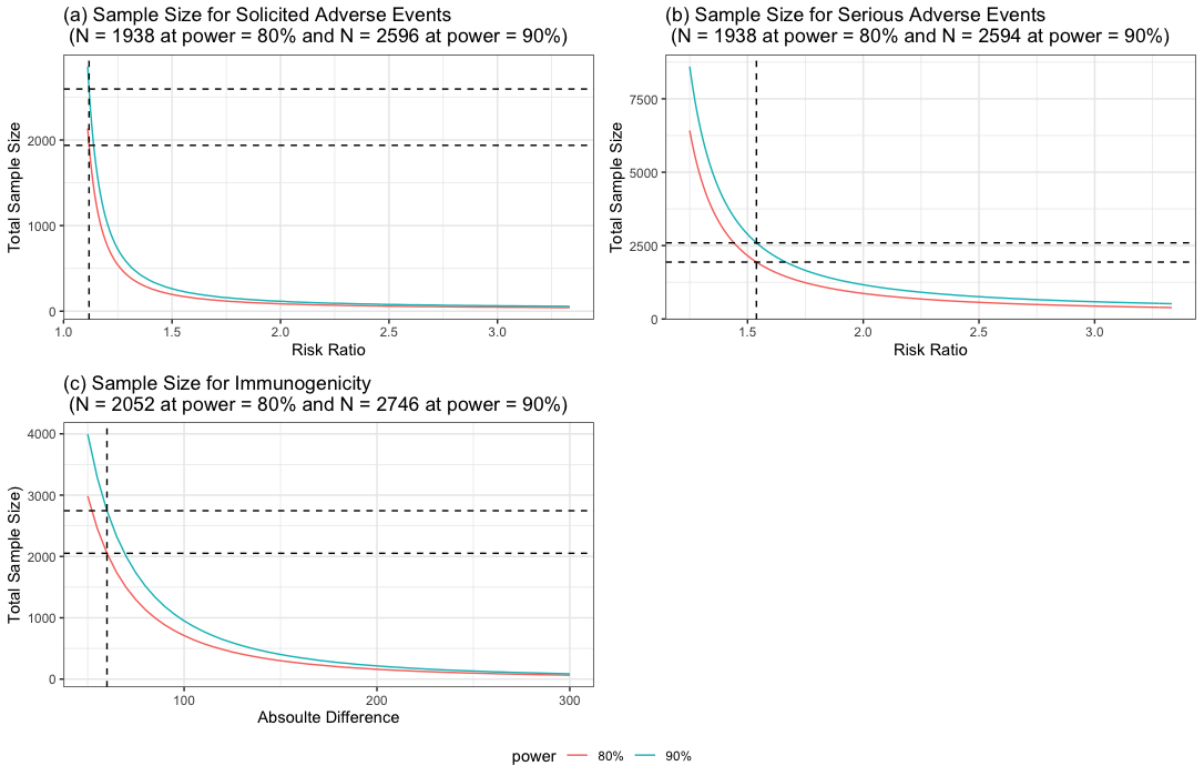

Figure 3: Sample sizes for determining differences in reactogenicity and immunogenicity outcomes between Ad26COVS1 and NVX-CoV2373 vaccine arms.

Feasible assumptions to support an approximate sample size of 1950 in comparing Ad26COVS1 versus NVX-CoV2373 in adults and NVX-CoV2373 mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents:

- Expected incidence of solicited and serious adverse events (AEs) in NVX-CoV2373 vaccine arm would be approximately 60% and 10% respectively.
- Expected mean logarithm of IgG would be at least 1000 (with a standard deviation of 500) in NVX-CoV2373 arm.
- Expected detectable risk ratio in solicited and serious AEs in NVX-CoV2373 arm (versus Ad26COVS1 arm) and NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents would be about 1.1 and 1.5 respectively.

- We expect little to no variation in AEs across the sites, hence no need to adjust the sample size by a design effect.

Conclusion

In our sample size computation, we conclude that a sample size of 1950 (n=1350 adults for HIV+ and n=300 for HIV- and 300 HIV positive adolescents) would be sufficient to evaluate the three primary objectives on reactogenicity and immunogenicity with sufficient power of at least 80% and 5% significance level between (i) HIV+ and HIV- participants and (ii) Ad26COVS1 and NVX-CoV2373 vaccine treatment arms. In the two scenarios, the derived assumptions commonly apply.

5 STUDY POPULATION

The target population for this Phase 2b study is HIV+ adolescents ≥ 12 to 17 years and HIV (+) and HIV (-) adults aged ≥ 18 to 64 years. Participants will be screened for eligibility criteria at the time of inclusion and may be enrolled anytime from 3months of completing their primary homologous vaccination series. Randomization will occur on day of vaccination and be 5-7 months following completion of the primary series for adult participants and ≥5 months after the primary series for adolescent participants consistent with US CDC and FDA recommendations and real-world setting. Randomization will be 1:1 to either the Janssen vaccine or Novavax vaccine within each primary vaccine platform for adult participants and Novavax or Pfizer/Moderna vaccine for adolescents. The duration of each adult participant's participation in the trial will be approximately 15-18 months depending on time of enrollment relative to boosting (subjects will be followed through for at least 15 mo post boost) and 12 months follow up for adolescents. Adherence to inclusion and exclusion criteria is essential to ensure safety to participants and precise comparison of groups. Waivers on inclusion and exclusion criteria are not allowed because they could jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety.

5.1 INCLUSION CRITERIA

To be eligible for the study, each HIV (+) participants must satisfy **all** of the following criteria:

1. Adolescent male or female aged ≥ 12 to 17 years at screening and adult male or female aged ≥ 18 to 64 years at screening (inclusive).

2. Written informed consent (and assent if adolescent), after review of the consent form and having adequate opportunity to discuss the study with an investigator or a qualified designee. For participants who cannot read or write, the consent must be witnessed by a literate third party not involved in study conduct.

3. Comply with study procedures, including potential home visits for COVID-19 follow-up.

4. Has completed a primary homologous vaccination series at least 3 months prior to enrollment. Vaccinations allowed include:

a) mRNA (Moderna mRNA-1273 or Pfizer/BNT) – primary series is 2 doses
b) Adenovector 26 (Janssen Ad26COVS1) – primary series is 1 dose;
c) Inactivated whole virus (Sinopharm-BIBP or Sinovac) – primary series is 2 doses;

5. Female participants of childbearing potential (defined as any female who has experienced menarche and who is NOT surgically sterile [i.e, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months or documented plasma follicle-stimulating hormone level ≥40 mIU/mL]) must agree to consistently use

an effective method of contraception from enrolment and agree to continue adequate contraception until 12 weeks after vaccination:

a. Condoms (male or female)
b. Diaphragm with spermicide
c. Cervical cap with spermicide
d. Intrauterine device
e. Oral or patch contraceptives
f. Hormonal Contraceptives implants or injection e.g., Norplant®, Depo-Provera®.
g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle.

NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. These procedures and laboratory test results must be confirmed by physical examination, by participant recall of specific date and hospital/facility of procedure, or by medical documentation of said procedure.

6. Medically stable at screening, as determined by the investigator (based on review of health status, vital signs, medical history, and targeted physical examination). Acceptable Vital signs as determined by the Principal Investigator or designee.

7. Receiving highly active antiretroviral therapy (HAART) and using the same regimen the past 8 weeks before screening. Changes in antiretroviral dosage within 8 weeks prior to entering the study are permitted. In addition, the exchange of pharmacological formulation (e.g., the conventional formulation for combination formulations) is allowed. If regimen has changed then the participant can be reconsidered for inclusion once the 8 weeks has passed.

8. An HIV-1 viral load < 1000 copies/mL and/or CD4 Count ≥ 200 cells/mm^3 within 3 months before randomization. May be taken during screening or utilize medical testing from clinic.

9. Documentation of HIV positivity by HIV rapid test or assay as per the Ministry of Health guidelines in the respective countries.

Each HIV (-) participant must meet all the following criteria to be enrolled in this study:

1. Male or female aged ≥ 18 to 64 years at screening, inclusive.

2. Willing and able to give informed consent prior to study enrolment and comply with study procedures, including potential home visits for COVID-19 follow-up.

3. Has completed a primary homologous vaccination series at least 3 months prior to enrollment. Vaccinations allowed include:

a. mRNA (Moderna mRNA-1273 or Pfizer/BNT) – primary series is 2 doses
b. Adenovector 26 (Janssen Ad26COVS1) – primary series is 1 dose;
c. Inactivated whole virus (Sinopharm-BIBP or Sinovac) – primary series is 2 doses;

4. Female participants of childbearing potential (defined as any female who has experienced menarche and who is NOT surgically sterile [i.e, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy] or postmenopausal [defined as amenorrhea at least 12 consecutive months or documented plasma follicle-stimulating hormone level ≥40 mIU/mL]) must agree to abstain from enrolment and through 3 months after the last vaccination OR agree to consistently use an effective method of contraception from enrolment and through 3 months after the last vaccination:

    a. Condoms (male or female)
    b. Diaphragm with spermicide
    c. Cervical cap with spermicide
    d. Intrauterine device
    e. Oral or patch contraceptives
    f. Hormonal Contraceptives implants or injection e.g., Norplant®, Depo-Provera®.
    g. Abstinence, as a form of contraception, is acceptable if in line with the participant's lifestyle.

NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. These procedures and laboratory test results must be confirmed by physical examination, by participant recall of specific date and hospital/facility of procedure, or by medical documentation of said procedure.

5. Medically stable at screening, as determined by the investigator (based on review of health status, vital signs, medical history, and targeted physical examination). Acceptable vital signs by PI.

6. Documentation of negative HIV rapid test (or assay) as per the Ministry of Health guidelines in the respective countries.

5.2 EXCLUSION CRITERIA

Participants with any of the following criteria will be excluded:

1. Use of a heterologous COVID-19 primary series at the platform level (mRNA, Adenovector and inactivated vaccine).

2. Use of an extended primary vaccination series or prior booster with any SARS-COV2 vaccine.

3. Any subject with prior Adverse Events of Special Interest Relevant to COVID-19 (see table 6).

4. Unstable or Severe Chronic disease inclusive of:

    a. Hypertension (elevated blood pressure [SBP>180mmHg or DBP>110mmHg]). Note that participants can be retested once after resting or return on another day for retesting. Participants may also have anti-hypertensive medication adjusted and may be reassessed after at least 2 weeks.

b. Congestive heart failure (CHF) stage 3 or greater or diagnosed cardiovascular disease that is not controlled using medication in the past 6 months.

c. Chronic obstructive pulmonary disease (COPD) with a history of an acute exacerbations repeated in the past 2 years. Note: If participant has been stable the last 6 months and are not Gold stage 3 or greater, they may be included.

d. Asthma stage 4 and/or unstable cases with asthma therapy adjustments in the past that 2 months.

e. Type 1 or any type 2 diabetes (adult onset) of severe grade by history/medical review or with an HbA1c > 8.5 in the last 6 months.

f. Chronic kidney disease requiring dialysis or GFR <30 (may use associated creatinine based on age and gender).

g. Chronic hepatic disease with evidence of hepatic compromise by history/medical review. Includes known Hepatitis B or C.

h) Chronic or serious neurological diseases (e.g. cerebrovascular disease (including transient ischemic attacks), autoimmune disorders, neurologic deterioration (including dementia), Guillain Barre syndrome).

i) Any ongoing, symptomatic acute illness requiring medical or surgical care or chronic illness of severe grade or that is not stable over the past 6 months (at the discretion of the investigator).

j) HIV Stage III/IV

5. Cognitive impairment – congenital or acquired

6. A child in care i.e., a child who is in the custody, care or guardianship of a director or a director of adoption.

7. Participation in research involving an investigational product (drug/biologic/device) within 30 days prior to first study vaccination and planned participation during this study. Exception is if participant in a follow up safety phase and the investigation product has been given > 6 months previously.

8. Prior receipt of an Ebola vaccine i.e., Ad26.ZEBOV/MVA-BN-Filo vaccines.

9. Received any other vaccine within 4 weeks prior to first study vaccination or planned vaccination within 4 weeks after study vaccination (including mass vaccination campaigns). Participants may be revaluated after the window has passed.

10. Any autoimmune or immunodeficiency disease/condition (iatrogenic or congenital), excluding HIV. Note: Stable endocrine disorders that have a confirmed autoimmune etiology (e.g., thyroid, pancreatic), including stable diabetes are allowed.

11. Chronic administration (>14 continuous days) of immunosuppressant, systemic glucocorticosteroids, or other immune-modifying drugs within 60 days prior to first study vaccination, excluding HAART. Note: An immunosuppressant dose of glucocorticoid is defined as a systemic dose ≥ 10 mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted.

12. Received immunoglobulin, blood-derived products, or other immunosuppressant drugs within 90 days prior to first study vaccination, excluding HAART.

13. Known disturbance of coagulation (iatrogenic or congenital). Note: The use of low-dose aspirin (≤ 325 mg/day) as prophylaxis is acceptable in dosages consistent with local standards of care, but the use of other platelet aggregation inhibitors, thrombin inhibitors, Factor Xa inhibitors, or warfarin derivatives is exclusionary, regardless of bleeding history, because these imply treatment or prophylaxis of known cardiac or vascular disease.

14. Any disease or disorder that would indicate a life expectancy less than 3 years such as active cancer.

15. Any known allergies to products contained in the investigational product or latex allergy or any history of anaphylaxis in relation to any previous vaccination.

16. Women who are breastfeeding or who are pregnant at the time of screening or plan to become pregnant within the first 12 months of the study.

17. A serious adverse event that occurs between screening and randomization. Subjects will not be allowed to be randomized.

18. History of alcohol abuse or drug addiction within 2 years prior to the first study vaccination.

19. Any condition (other than HIV) that, in the opinion of the investigator, would pose a health risk to the participant if enrolled (including neurologic or psychiatric conditions deemed likely to impair the quality of safety reporting).

20. Study team member or first-degree relative of any study team member (inclusive of sponsor, and site personnel involved in the study).

Temporary exclusions:

21. Acute respiratory and/or non-respiratory illness or documented temperature of > 38°C in the past 24 hours. Note: Participant may be re-evaluated after symptoms have resolved for at least 3 days.

22. Positive RT-PCR SARS-CoV-2 test during screening or at time of randomization. Subject must be SARS-COV-2 symptom free and have a negative test prior to randomization.

23. Documented severe SARS-CoV-2 infection in the last 3 months. May be rescreened when this period has passed.

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but during the screening process meet an exclusion criterion or fail to meet an inclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) that occurred during the screening period. Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once as appropriately noted in the exclusion criteria. Rescreened participants should be assigned the same participant number as for the initial screening. Screening will remain open until the randomization assignments are fulfilled. It is possible participants may be screened and are eligible but are not randomized to the study due to either temporary waiting periods or excess number of participants that qualify for randomization.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

5.4.1. COMMUNITY INFORMATION

The community in which the study will take place will be informed about the nature and design of the study. Community leaders (including chiefs, local village elders, and opinion leaders as applicable), Community Advisory Board members, local and national health authorities will be formally briefed in their own language on the nature and purpose of the study. They will have the opportunity to ask questions of the PI or his designees.

5.4.2. RECRUITMENT

Participants will be recruited with methods that are in accordance with ICH-GCP standards, other policies and regulations of the governments of Kenya, Rwanda and the Democratic Republic of Congo. Recruitment activities will be implemented in coordination with Ministry of Health (MoH), community, civil society, and other stakeholders to address and meet local needs and expectations, and to achieve community support. Adolescents 12-17 years and adults 18-64 years will be identified and recruited from the HIV patient cohorts in the health facilities and for the HIV negative adults, from the households in the surrounding communities at the respective study sites. Depending on the site practice, potential

participants identified from within these locations will be approached at the clinic or in the community using a recruitment script depending on site practice by study staff delegated to carry out recruitment. Informed consent and assent will be administered in accordance with the protocol, ICH-GCP guidelines and country guidelines. Language and illiteracy will not be impediments in the recruitment process, all briefings and explanations will be in the understandable language of the participant. It is expected that not more than 2,400 HIV (+) participants will be screened to identify 1,650 to randomize (30% failure rate). The failure rate for HIV (-) participants is expected to be about 25%.

Community engagement will be conducted to identify community organizations in each sector that may potentially serve as recruitment and referral sites. Community support of the study will be sought through community engagement activities including ongoing communication with community leaders, established community groups, local Ministry of Health leadership, and where applicable involvement of the local Community Advisory Board (CAB) or equivalent. Community Health Workers will also assist with community sensitization and mobilization. Another community engagement strategy will be through use of small group or informal gatherings. These will involve fewer people and may target less represented group of people within the larger community e.g., adolescents and young women.

Study staff may also recruit study participants through HIV care and treatment clinics, and outpatient hospital clinics. Prior to recruiting from a facility or clinic, the study team will engage the MoH leadership of the facility (with the permission of the MOH leadership) and will sensitize MoH Staff at the facility about the study.

Once potential participants have been identified by study staff, they will be given a brief overview of the study, and those who are interested in participating in the study will be referred to study staff at the respective Clinical Research Centers for further briefing. If participants remain interested, they will engage in the informed consent process and then formal screening will begin.

6 STUDY PRODUCT AND ADMINISTRATION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol. Details of dosage, preparation, handling, storage, labelling, etc will be provided in the study pharmacy manual.

6.1.1 DESCRIPTION OF STUDY PRODUCTS

6.1.1.1. JANSSEN AD26COVS1 (COVID-19) VACCINE

Janssen Ad26COVS1 is formulated to contain: recombinant, replication-incompetent adenovirus type 26 expressing the SARS-CoV-2 spike protein, citric acid monohydrate, trisodium citrate dihydrate, ethanol, 2-hydroxypropyl-β-cyclodextrin (HBCD), polysorbate-80, sodium chloride. Janssen Ad26COVS1 vaccine components are provided in multi-dose vials at a concentration of 1×10^{11} vp/mL, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp. A multi-dose vial may be used on more than one occasion within a single clinic day.

6.1.1.2. NOVAVAX NVX-COV2373 (COVID-19) VACCINE

Novavax NVX-CoV2373 vaccine is a recombinant SARS-CoV-2 nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. The vaccine components are provided in multi-dose vials. The dose level will be 5 µg SARS-CoV-2 rS with 50 µg Matrix-M1 adjuvant (mixed in clinic or previously co-formulated). A multi-dose vial may be used on more than one occasion within a single clinic day, not to exceed 6 hrs. from first use (based on WHO multidose open vial policy).

6.1.1.3. MRNA (MODERNA MRNA-1273 OR PFIZER/BNT) VACCINES

The Pfizer–BioNTech COVID-19 vaccine, BNT162b2, is an mRNA vaccine encoding a P2 mutant spike protein (PS 2) and formulated as an RNA–lipid nanoparticle of nucleoside-modified mRNA (modRNA). BNT162b2 elicits a blunted innate immune sensor activating capacity and thus augments antigen expression. Encapsulation into LNPs allows transfection of the mRNA into host cells after intramuscular (IM) injection. During mixing of the RNA and the dissolved lipids, the lipids form the nanoparticles encapsulating the RNA. After injection, the LNPs are taken up by the cells, and the RNA is released into the cytosol, where it is translated into the encoded viral protein. The mRNA is rapidly degraded intracellularly, while the resulting peptides are presented at the cell surface, triggering a specific humoral T-cell-mediated immune response with activity against the spike protein

Moderna's mRNA-1273 COVID-19 vaccine is an LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein. The vaccine contains a synthetic mRNA (single-stranded, 5'-capped)

encoding the prefusion-stabilized spike glycoprotein (S) of SARS-CoV-2 virus. The vaccine also contains the following ingredients: lipids (SM-102, 1,2-dimyristoyl-rac-glycero-3- methoxy polyethylene glycol-2000 (PEG2000-DMG), cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)), tromethamine, tromethamine hydrochloride, acetic acid, sodium acetate, and sucrose. The Moderna COVID-19 vaccine is supplied as a frozen suspension, at between -25^{0}C and -15^{0}C, in a multidose vial containing 10 doses. The vaccine is a white to off-white, sterile, preservative-free frozen suspension for intramuscular injection. The vaccine must be thawed prior to administration. After thawing, a maximum of 10 doses (0.5 ml each) can be withdrawn from each vial. Vials can be stored refrigerated at 2–8°C for up to 30 days prior to first use. Unopened vials may be stored at 8–25°C for up to 12 hours. After the first dose has been withdrawn, the vial should be held at 2–25°C and discarded after 6 hours.

6.1.2 DOSING AND ADMINISTRATION

Date and time of study vaccine administration, and arm of injection must be captured in the source documents and the eCRF. Vaccine doses will be prepared in a clinical pharmacy under aseptic conditions. Detailed instructions for the preparation, storage and handling of study vaccine will be provided in a Pharmacy Manual.

Adult study participants will be randomized to receive either a single dose of Janssen Ad26COVS1 or Novavax NVX-CoV2373 vaccine at day 0. Adolescent study participants will be randomized to receive either a single dose of Novavax NVX-CoV2373 or mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines at day 0. Study vaccine will be administered by IM injection (0.5 ml) into the deltoid muscle, preferably of the non-dominant arm. If an injection cannot be given in the deltoids due to a medical or other contraindication (for example, tattooed upper arms rendering it difficult to assess site reactogenicity), use alternative locations will be considered. In all circumstances, IM injections in other locations than the upper arm are not considered protocol deviations. The location of injection will be documented in the source documents and the eCRF. All vaccinations will be administered on an outpatient basis by designated site personnel in a way to maintain the blind. The unblinded pharmacist or assigned site personnel involved in study drug preparation or management will not otherwise be involved in the study procedures or clinical observation of participants.

6.2 PACKAGING, LABELLING, STORAGE, AND HANDLING OF STUDY PRODUCTS

Each study intervention (vial) and each box will bear a fixed label containing the dose number. All will be labeled in accordance with regulatory authority requirements.

All investigational products must be stored according to the label instructions in a secure room with restricted access by authorized study personnel only. Each site will be required to keep a temperature log to establish a record of compliance with storage conditions.

Janssen Ad26COVS1 vaccine components are provided in multi-dose vials at a concentration of 1×10^{11} vp/mL, with an extractable volume of 0.5 mL, and dosed at 5×10^{10} vp. The product will be stored unpunctured at 2°C to 8°C (36°F to 46°F) and will be protected from light. After the first dose has been withdrawn, the vial should be held between at 2°C to 8°C for up to 6 hours in compliance with WHO Multidose open vial policy. Any remaining dose of opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

The Novavax NVX-CoV2373 SARS-CoV-2 rS vaccine with Matrix-M1 adjuvant is stored and stable at 2°-8°C. After the first dose has been withdrawn, the vial should be held between at 2°C to 8°C for up to 6 hours in compliance with WHO Multidose open vial policy. Any remaining dose of opened vial must be discarded after 6 hours or at the end of the immunization session, whichever comes first.

The Pfizer/BNT) vaccine are provided in multidose vials at a concentration. Unpunctured vaccine vials may be stored in ultra-cold freezer between -90°C and -60°C until the expiration date or may be stored in the refrigerator between 2°C and 8°C (36°F and 46°F) for up to 10 weeks. Vaccine vials should be store upright in the tray or box protected from light. Punctured vials after withdrawal of the first dose may be stored between 2°C and 25°C for up to 12 hours in compliance with WHO Multidose open vial policy. All remaining vaccine vials must be discarded after 12 hours or at the end of the immunization session, whichever comes first.

Moderna mRNA-1273 vaccine vials may be stored unpunctured in the freezer at -50°C to -15°C until the expiration date or in the refrigerator between 2°C and 8°C for up to 30 days. Store vials upright in the tray or box, protected from light. Punctured vaccine vials after withdrawal of the first dose should be stored between 2°C and 25°C for a maximum of 8 hours in accordance with WHO multidose open vial policy. Discard vial and any remaining vaccine after 12 hours (8 hours for Bivalent Pink capped yellow-bordered vial) at the end of immunization session.

If study vaccine is exposed to temperatures outside the specified temperature range, the affected vaccines will be quarantined, and all relevant data will be sent to the sponsor to determine if the affected supplies can be used or will be replaced. Vials will be used for multiple participants per day but at the end of the expiry time any unused product from an opened vial will be retained for disposal and not used further. Both used and unused vaccine vials and syringes will be stored at the site and made available to the unblinded monitor for verification before destruction/return to sponsor. Additional information will be provided in investigational brochures and pharmacy manual.

The investigator at each site is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The actual study vaccine administered to the participant must be documented on the vaccine accountability form or within the IVRS or IWRS system that can track study vial used. All study vaccine will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study vaccine containers.

Study vaccine must be handled in accordance with the protocol and the container label and must be stored at the study site in a limited-access area.

Unused study vaccine must be available for verification by the sponsor's unblinded site monitor during on-site monitoring visits. The local destruction or return to the sponsor of unused study vaccine will be documented on the vaccine accountability form. When the study site is an authorized destruction unit or has access to authorized destruction unit and study vaccine supplies are destroyed on-site/in-country, this must also be documented on the vaccine destruction form. Potentially hazardous materials containing hazardous liquids, such as needles should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes. The vaccine syringes will be retained and stored after vaccine administration for purposes of accountability by the pharmacy (unblinded) study monitor.

Study vaccine should be administered under the supervision of a qualified member of the study-site personnel or pharmacist trained to perform vaccinations. Study vaccine will be administered only to study participants. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study sites agreed upon with the sponsor.

The investigator (or designee) will maintain accurate records of receipt of all investigational product, including dates of receipt and documentation of cold chain requirements. At the completion of the study, and to satisfy regulatory requirements regarding investigational product accountability, all investigational products will be reconciled and retained or destroyed according to applicable regulations. No investigational product will be destroyed until authorized in writing by the sponsor.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 PROCEDURES FOR RANDOMIZATION AND STRATIFICATION

Treatment assignment will be based on a computer-generated randomization schedule will be prepared by the Sponsor statistician. Adult participants will be randomly assigned in a blinded manner using a centralized Interactive Response Technology (IRT/IWRS) in a 1:1 ratio to receive either the Novavax NVX-CoV2373 or Janssen Ad26COVS1 vaccine within primary treatment platform and by strata of age and HIV status within country. Adolescent participants will be randomized in 1:1 ration to receive either Novavax NVX-CoV2373 and mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines.

The randomization of adult participants will be balanced by using randomly permuted blocks and will be stratified by: HIV (+) adults age group (18-45, 46-64 with a 2:1 ratio) within each primary platform with equal representation of the 3 primary platforms. All 3 countries will participate in adult recruitment with a goal of 2:1:1 contribution of participants from Kenya, DRC and Rwanda. However, adjustments for country level enrollment may be needed to achieve the age strata and the primary vaccine series distribution and study enrollment target. In addition, a group of 300 HIV (-) adult participants (aged 18-64) will be enrolled who have received a homologous primary series from one of the three platforms (~100/primary platform), with a goal of similar ratio of country recruitment.

As adolescents may not have received similar vaccine distribution as adults, stratification will not occur and representation by country and primary vaccine platform is more uncertain. Therefore, a maximum of 300 adolescents for the mRNA primary platform will be planned. However, adolescent immunogenicity data will be analysed both overall and also considering the time of boost (≥5-12 or >12 months) post primary vaccination. Unequal distribution of primary vaccine platform for adolescents between participating countries is expected.

The IRT/IWRS will assign a unique intervention code, which will dictate the intervention assignment for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IRT/IWRS and will then give the relevant participant details of treatment assignment to uniquely identify the participant. Information regarding the IRT/IWRS procedure will be provided to the sites.

A subset of HIV (+) (maximum of 60/primary vaccine platform) and HIV (-) (maximum of 30/primary vaccine platform) adult participants from the Kenya site will contribute to CMI subset based on consenting (opt in) and will be stratified between the arms in each vaccine platform. This subset will only involve HIV (+) and HIV (-) adult participants aged 18-64 because of the required blood volumes and will only be conducted in Kenya to ensure standardization of the procedures for PBMC processing, operational efficiency, and experience of the immunology lab.

6.3.1.1 BLINDING PROCEDURES

This is a double blinded study. The unblinded site personnel will manage study vaccine logistics, preparation, dispensing and administration so as to maintain the blind from the remainder of the site personnel and participants. The unblinded site personnel will not be involved in study-related assessments or have participant contact for data collection following study vaccine administration.

Randomization codes will be maintained within the IRT/IWRS, which has the functionality to allow the investigator to break the blind for an individual participant. Data that may potentially unblind the study vaccine assignment (e.g., immunogenicity data, study vaccine accountability data, study vaccine allocation, or specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained at the participant level and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, sponsor, clinical team, or others as appropriate until the time of database lock and unblinding.

Vaccines will be handled to maintain the study vaccine in a blinded manner by the unblinded drug accountability team. This many include providing a masked syringe to the blinded vaccine administrator or using an unblinded drug accountability team member who performs the injection and then hands the participant over to the blinded team for further evaluation. In either case the vaccinator is a trained and qualified study nurse, medical doctor, otherwise qualified Health Care Professional who will perform the injection.

6.3.1.2 BREAKING THE BLIND

A participant's study vaccine assignment will not be broken until the end of the study unless medical treatment of the participant depends on knowing the study vaccine the participant received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual participant's study vaccine allocation. Whenever possible, the investigator should contact the medical monitor to discuss the medical emergency and the reason for revealing the actual study vaccine received by that participant. If the investigator cannot contact the medical monitor in a timely manner the blind may be broken by the investigator. The medical monitor should be contacted as soon as feasible after the unblinding. The study vaccine assignment will be unblinded through IRT/IWRS. Reasons for study vaccine unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken together with the identity of the person responsible must also be documented. The blind may also be broken in the event of a Suspected Unexpected Serious Adverse Reaction (SUSAR) to determine regulatory reporting. In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for planned interim analyses prior to study completion. All data will be analyzed separately from the point of unblinding for safety, immunogenicity and efficacy, as described in the Statistical Analysis Plan.

In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented in the IRT/IWRS and in the source document. The documentation received from the IRT/IWRS indicating the code break must be retained with the participant's source documents in a secure manner. Participants who have had their intervention assignment unblinded should continue to return for scheduled safety evaluations at a minimum. They may also contribute to immune sampling, but their data will be handled in the appropriate manner as outlined in the Statistical Analysis Plan. All data will be analyzed for safety, immunogenicity, and efficacy as described in the Statistical Analysis Plan for both interim and final analyses. The Statistical analysis plan will be approved prior to the first interim analysis.

6.3.2. STUDY VACCINATION PAUSING RULES

Adverse events that may lead to the study vaccination pausing rules are described below and will be assessed by the DSMB to confirm that the study pause is warranted.

The occurrence of any of the following events will lead to a pause in further study vaccination and a review by the DSMB:

- Death of a participant, considered related to study vaccine or if the causal relationship to the study vaccine cannot be excluded, OR
- One or more participants experience an SAE that is determined to be related to study vaccine or by causal relationship to the study vaccine cannot be excluded, OR
- Multiple grade 3 reactogenicity events following booster vaccination that exceed that specified in the product investigator brochure or >10% grade 3 (*whichever is higher*) for any reactogenicity events by primary vaccine platform OR

- If a PI, Safety Monitor or Sponsor requests the DSMB to convene because of concerns about safety in the study

To enable prompt response to a situation that could trigger pausing rules, the investigator should notify the sponsor's medical monitor, immediately and no later than 24 hours after becoming aware of any death or a potentially related SAE AND update the eCRF with relevant information on the same day the SAE information is collected. Based on the pausing criteria, the sponsor's medical monitor or designee, then decides whether a study pause is warranted and informs the DSMB of the decision. In the case of the grade 3 reactogenicity events the safety/medical monitor will be informed/monitor for pause criteria being met. The sponsor's medical monitor or designee or the investigator(s) (upon consultation with the sponsor's medical monitor or designee) may initiate DSMB review for any single event or combination of multiple events which, in their professional opinion, could jeopardize the safety of the participants or the reliability of the data. All sites will be notified immediately in the event of a study pause. If vaccination is still ongoing, it will be paused and visit schedules will be adjusted so as not to induce protocol violations. The coordinator of the DSMB is responsible for notifying DSMB members and coordination of a DSMB meeting in the event of a study pause. Resumption of vaccinations will start only upon receipt of written recommendations by the DSMB. The clinical site(s) will be allowed to resume vaccination activities upon receipt of a written notification from the sponsor. The formal recommendation from the DSMB will be forwarded by the investigator to the ERC/IRB and by the sponsor to the relevant health authorities, according to local standards and regulations. Vaccinations for the study may be suspended for safety concerns other than those described above, or after review during standard DSMB meeting if participant safety may be threatened.

In addition, the DSMB will meet quarterly after enrollment is completed to review unblinded safety data including breakthrough confirmed SARS-CoV2 cases. They may also be asked to include in their review any available immunogenicity data following interim database locks should there be concerns of waning immunity relative to breakthrough cases or to ongoing new data generated in the field of COVID-19. The DSMB may recommend modifications to the protocol or stopping of the study early. The sponsor has the final authority to accept the DSMB recommendations. Details of the DSMB functioning are described in the DSMB Charter.

6.4 STUDY INTERVENTION COMPLIANCE

All doses of the study vaccine should be administered at the site under direct observation by delegated qualified study personnel. Details of vaccine administration will be recorded in the source document and eCRF. The location (i.e., right or left arm), date, and timing of all doses of study vaccine will be recorded in the participants' source document and eCRF. If a participant is not administered study vaccine, the reason for the missed dose will be recorded.

6.5 CONCOMITANT THERAPY

Concomitant medications, treatments and procedures will be recorded on the source document and documentation in the eCRF of ongoing concomitant medication(s) will be limited to specific categories of medication(s) being taken due to chronic conditions or associated with adverse events being collected. Of

note, given the population being studied, all HAART will be recorded at each visit for HIV + participants and changes in HAART therapy during the trial be documented. Adverse events being collected on a given visit will have associated medications recorded. Administration of all vaccines during trial participation will be recorded in the source document and eCRF. Prescription and over the counter (OTC) drugs, as well as herbals, vitamins, and supplements, will be included as designated according to the adverse event monitoring schedule.

Antipyretics may be recommended post-vaccination for symptom relief as needed. During the study, the use of investigational vaccines other than the study vaccine is not allowed. Treatment with investigational COVID-19 drugs after diagnosis of a COVID-19 case is allowed during the follow-up period and needs to be recorded in the COVID-19-episode description.

Licensed vaccines can be given at least 28 days before or at least 28 days after a study vaccination. Exceptions are when medically needed (e.g., yellow fever, rabies, tetanus), it must take priority over the study vaccine windows and should be documented in the source document and eCRF. Participants should not receive additional COVID-19 vaccines once they are enrolled in the trial because it would impact the scientific validity of the study. However, participants are at liberty to voluntarily decide whether or not they would like to receive any licensed COVID-19 vaccines and such receipt should be recorded in the concomitant medication/vaccination eCRF.

Documentation of any prohibited therapies administered (medications/vaccinations) may result in removal of such subjects for specific immunogenicity analyses. Depending on the time of the occurrence, any participant who receives a prohibited concomitant therapy will not be included in the per protocol immunogenicity analyses.

7 PARTICIPANT COMPLETION AND WITHDRAWAL

7.1 PARTICIPANT WITHDRAWAL FROM THE STUDY

A participant who returns for the concluding visit at Month 15-18 post booster is considered to have completed the study.

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- Study participants who withdraw from the study i.e., "withdrawal" will not be replaced unless the withdrawal is prior to the booster dose of study vaccine and randomization remains open.
- Study participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. All attempts will be done by the investigator to follow study participants who have received a dose of study vaccine until the end of the study. The investigator may request that the study participant complete safety evaluation or study procedures prior to withdrawal.
- Information related to the withdrawal will be documented in the source document and eCRF. The Investigator will document whether the decision to withdraw a study participant from the study was made by the participant or by the Investigator, as well as which of the following possible reasons was responsible for withdrawal:

    - COVID-19-related AEs (specify)
    - COVID-19-related SAEs (specify)
    - Non-COVID-19-related AEs (specify)
    - Non-COVID-19-related SAEs (specify)
    - Death
    - Lost to follow-up
    - Physician decision (specify)
    - Pregnancy
    - Protocol deviation
    - Study terminated by Sponsor
    - Withdrawal of consent by participant* (specify)
    - Other (specify)

*In a case where a participant is withdrawn from the study because they have withdrawn consent, though not mandatory, the investigator will endeavor to document the reason for withdrawal of consent, if specified by the participant, in the eCRF.

- Should study participant request to be withdrawn from the study because of an AE, the investigator will try to obtain an agreement to follow up with the participant until the event is considered resolved or stable and will then complete the end of study eCRF. Study participants

who have been withdrawn from the study because of AEs (including SAEs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow up with participants who are withdrawn from the study as result of an SAE or AE until resolution of the event or until the event has subsided, stabilized, disappeared, or until the event is otherwise explained, or the participant is lost to follow-up.

- Investigators will make an attempt to contact those participants who do not return for scheduled visits or follow-up. Only after 3 unsuccessful attempts at contact can a subject be considered lost to follow up. This should include one attempt by a community worker to visit the subject in their home (or local equivalent).
- If the study participant withdraws from the study and also requests withdrawal of his/her consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data and samples collected before such withdrawal of consent i.e., all data collected until the date of withdrawal/last contact of the participant will be used for the analysis.
- If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and comply.
- The Sponsor will continue to retain and use all research results and/or data that have already been collected for the study evaluation, unless the participant has requested destruction of these samples and data. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).
- From an analysis perspective, a 'withdrawal' from the study refers to any participant who did not come back for the concluding visit/was not available for the concluding contact foreseen in the protocol. A study participant is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this participant from the date of withdrawal/last contact.
- Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved. Should pregnancy occur in the study it is advisable that the participant continue in the study to be monitored and a pregnancy notification form and outcome of the pregnancy and infant should be recorded.
- Participants who withdraw, are withdrawn or terminated from this study, or are lost to follow-up after signing the ICF but prior to study vaccination may be replaced.
- Whenever possible, it is desired that participant remain in the study to be followed for safety. It is highly encouraged to allow safety follow up to be achieved for participant constraints (e.g., phone follow up) rather than to have a participant withdrawal from the study.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for at least 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as per the study visit window and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls, home visit if necessary, or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 INFORMED CONSENT, RECRUITMENT, SCREENING ND OTHER STUDY PROCEDURES

At the beginning of the study, potential participants will be approached using a recruitment script at the HIV treatment, care clinics within the Hospitals, health facilities within the study areas or any site recruitment facility by study staff delegated to carry out recruitment activities. Prior to any volunteer joining the study, a briefing session with a review of inclusion and exclusion may be completed to minimize the number of screen failures and ensure participants have interest to participate. The study staff will brief the participants and their parents/legally acceptable representatives (LAR) for those below 18 years (or age appropriate based on national guidelines and referenced herein as 'below 18 years) individually or in small groups about the study with the aid of study briefing materials (study information leaflet) and may also use the informed consent document to review critical information. At the end of the briefing, questions will be addressed. This will enable participants and their parents/LAR to understand the purpose of the study as well as the study procedures. They will be given adequate time to think about participating, ask any questions and decide whether they want to participate or not. Thereafter, the informed consent review will be completed and a signature on the written informed consent document will be obtained from each individual who wants to participate in the study. The participant and their parents/LAR for those below 18 years and the study staff conducting informed consent and assent explanation will sign and date the consent and assent forms. The participant signature confirms that (s)he has understood the information. For illiterate individuals, the informed consent process will be conducted in the presence of an impartial witness. The participant and their parents/LAR for those below 18 years will thumb print the consent form and assent form and the witness will sign and date the form. Each participant's consent and assent forms will be kept in their study folder and a copy will be given to the participant to take home on the same day. The study team will use the participant's preferred language usually English, French, or local language for both consent and assent depending on the study site. In case of any amendments to the protocol resulting in changes in study procedures, the participant will be informed, and additional informed consent and assent will be obtained if necessary. Formal screening will only commence once informed consent has occurred. In accordance with Good Clinical Practice, the volunteer may terminate participation in the study at any time for any reason without penalty. Additionally, in the event that the participant is unable or unwilling to adhere to the protocol design, the investigator may terminate participant's participation.

Screening procedures are to be completed as shown in the Study Schedule of Events (Table 1).

Screening procedures include (but are not limited to); vital signs, medical history, concomitant medications, demographics, physical examination, standard laboratory screening tests (Complete Blood Count (CBC) including Hemoglobin, White Blood Cells and, Platelets, Creatinine, ALT, AST, HIV rapid test), and in HIV (+) subjects: HIV viral load and CD4 count. A urine/serum pregnancy test will be performed on all female participants of childbearing potential. Certain exclusions allow rescreening. Participants excluded from this study because of significant abnormalities not previously known by them will be

referred to an appropriate health provider for evaluation and treatment. Vitals signs will be collected in at the time of screening, prior to and 30-60 minutes following vaccination and at any other visit if medically indicated and scored by FDA toxicity grading (Table 4). For adolescents, FDA toxicity scoring will be applied for fever only. Information gathered during screening (medical history, physical examination, and laboratory analysis) will be recorded in the Source Documents and the eCRFs.

Table 4: FDA Toxicity Scoring of Vital Signs for Adults. Adolescents to have FDA Scoring for Fever only.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	39.0 – 40	> 40
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

*vital signs to be taken at rest.

**no hot or cold beverages or smoking for at least 15 min prior to temperature reading.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations.

The principal investigator or designee will determine the eligibility for all participants after reviewing the results. A study identification document (may include photograph) will be made of each participant who is screened. The participants will bring the study identification cards whenever they visit the research clinic for checkup(s).

8.2 STANDARD OF CARE STUDY PROCEDURES

For the duration of their participation in the trial, all participants will receive essential health care in accordance with National Ministry of Health guidelines. Treatment and care for COVID-19 will primarily be through respective country MoH facilities in accordance with national guidelines. However, if inpatient care is required and if the capacity of the MoH facilities is overwhelmed and unable to provide necessary care to the volunteer, the site will strive to arrange for alternative care at an appropriate faith based or private health facilities as deemed appropriate to the extent possible with the current COVID-19 bed capacities.

8.3 LABORATORY PROCEDURES AND EVALUATION

Laboratory samples will be collected primarily at the study site as per the laboratory manual of procedures. During the surveillance for symptoms of COVID-19-like illness, participants will notify investigators about the onset of COVID-19-like symptoms, if they had known exposure to a COVID-19 positive contact or if they had a positive COVID test from any other source. Participants will have samples collected in the field or be asked to visit the site for the collection of rapid antigen testing (and confirmatory RT-PCR by nasopharyngeal swab for any positive rapid tests). If confirmed as positive by rapid Ag testing, participants will undergo a nasopharyngeal sample for RT-PCR and complete daily reporting of their symptoms in the paper diary through 10 days post test. Should participants have a positive RT-PCR test, they will undergo genomic sequencing analysis for VOC if their CT value is significant.

Blood samples will be collected using kits and supplies provided and following an aseptic technique with minimization of discomfort. Nasal secretory samples will be collected using Nasosorb kit. All samples should follow collection and processing according to the laboratory manual of procedures. All biological materials collected will be handled according to established SOPs for the protection of participants and study staff.

8.3.1 CLINICAL LABORATORY EVALUATIONS

The clinical laboratories at the sites will process the blood samples for: CBC (Hgb, WBC, PLT), creatinine, ALT, AST, AIC (if required by exclusion criteria), HIV rapid test, participant viral loads and CD4 cell count (for HIV positive participants), FSH (optional), SARS-CoV-2 Rapid Antigen, RT-PCR test and pregnancy test where applicable.

8.3.2 SPECIMEN PREPARATION, HANDLING AND STORAGE

Samples will be prepared, handled, and stored according to the laboratory procedures manual and site laboratory SOPs as applicable. All samples will be labeled with appropriate unique identifiers. Documentation of samples will include such information as participant ID number, date/time of collection, study designee, aliquot number and any other data required by testing facility (e.g., bar codes). Samples being shipped to another laboratory for performance of an assay will be sent from the study site to the performing lab, while maintaining appropriate temperatures according to laboratory procedures manual and site SOPs as applicable. A chain of custody will be maintained both at the sending lab and the receiving lab. Local storage of specimens (e.g., serological or respiratory samples) will be at appropriate temperatures and according to local SOP.

8.3.3 SPECIMEN SHIPMENT

The study immunological samples will be analyzed at a laboratory within CEPI Central Lab Network at the International Center for Diarrhoeal Diseases Research in Bangladesh (ICDDRB), 68, Shaheed Tajuddin Ahmed Sarani Mohakhali, Dhaka 1212, Bangladesh. Immunological assays will include ELISA, viral

neutralization antibodies and Cell Mediated Immunity (CMI). The immunology test samples to be transported to ICDDRB will include serum for IgG ELISA, mucosal swabs for IgA ELISA, serum for Pseudo-neutralization antibodies and peripheral blood mononuclear cells (PBMC) samples for CMI by ELISPOT.

8.4 SCHEDULED STUDY VISITS

All visits completed according to the Schedule of Event (SOE) as shown in Table 1 above.

8.5 UNSCHEDULED VISITS

Any participant visit to the study sites or evaluation by study staff at a health facility that takes place outside of the scheduled visits will be considered an unscheduled visit. Any medical issues discovered at an unscheduled visit will be evaluated, treated, and/or referred as appropriate and their encounter documented on source documents and entered into the eCRF as an unscheduled visit. Appropriate CRFs will be utilized as deemed necessary for any unscheduled visit.

In the case of SARS-CoV-2 symptoms or known exposure, subjects will be brought in for a rapid antigen test. Any time a SARS-CoV-2 rapid antigen test is positive, subjects will have a nasopharyngeal swab taken for confirmation by RT-PCR. Subjects will be dispensed a COVID-19 symptom diary to be completed daily for 10 days. They will be scheduled for a follow up visit (unscheduled visit) between 10-14 days and will return their diary and get retested by SARS-CoV-2 rapid antigen. Should symptoms still be present another COVID-19 symptom diary will be dispensed. If rapid Antigen remains positive or subjects have another COVID-19 symptom diary dispensed, then they will be rescheduled in another 10 days for repeat testing/diary review. This will occur until subjects are both symptom free as well as rapid antigen negative.

8.6 SAFETY AND OTHER ASSESSMENTS

The principal investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE), treatment emergent adverse event (TEAE), adverse event of special interest (AESI) or serious adverse event (SAE). Each participant will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. Of note, participants should notify the site immediately if they record a grade 3 reactogenicity event and should be evaluated within 24 hrs. to confirm the severity.

8.6.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS - DEFINITION AND CLASSIFICATION

8.6.1.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence following the use of a medicine product or intervention, whether or not considered causally related to that use. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. The occurrence of an adverse event (AE) may come to the attention of study personnel during study visits and interviews of a study

participant presenting for medical care, or upon review by a study monitor. In vaccine studies, solicited adverse events (local and systemic) are proactively collected after vaccination (before exit from clinic) and daily for 7 days afterwards (see section 8.6.2.1).

All AEs occurring within the 28 days following vaccination must be recorded. All Treatment Emergent Adverse Events (TEAE) through 85 days are to be recorded. Serious adverse events (SAE) and Adverse Events of Special Interest (AESI) are to be recorded from the time of randomization and vaccination until EOS as shown on Table 1: Study Schedule of Events. In the case of participants who are screened but never randomized, any medical event/illness will be captured as part of Medical History and stored in the screen failure documentation. The occurrence of an AE, TEAE, AESI or SAE may come to the attention of study personnel during study visits and field worker visits. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product, and date of resolution/stabilization of the event. All AEs that are required to be identified during a specific study visit interval will be followed to adequate resolution, until stable (which may include a new baseline status) or until EOS.

All AEs either observed by the investigator or a member of the study team or reported by the participant spontaneously or in response to a direct question will be evaluated by the investigator as outlined in the schedule of events. The nature of each event, date and time of onset (where appropriate), outcome, intensity and relationship to drug administration should be established. Details of any supportive treatment given should be recorded on the appropriate page of the CRF. When an AE occurs, it is the responsibility of the investigator to review all documentation relative to the event and ensure appropriate detail is documented in the source documents.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

Any medical condition that is present at the time that the participant is screened will be considered as baseline Medical History and not reported as an AE. However, if the study participant's medical condition deteriorates at any time during the study, it will be recorded as an AE.

Maximum severity of an AE will be documented in addition to the duration of the event. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AEs (those being monitored at the time) since the last visit, in accordance with the adverse events being collected at that timepoint. Any interventions required to treat a disease or condition in an enrolled participant will be allowed. Treatment of any AE is at the sole discretion of the investigator in accordance with the local treatment guidelines and clinical practices. Any medication administered for the treatment of an AE should be recorded in the participant's eCRF.

The PI/designee will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention in the supporting study documents such as the protocol and investigator brochure (IB). Suspected Unexpected Serious Adverse Reactions (SUSAR) are reportable to authorities similar to SAEs.

8.6.1.2 SEVERITY OF ADVERSE EVENT

The guideline below will be used to describe severity of AEs.

- **Grade 1; Mild** – Events require minimal or no treatment and does not interfere with the participant's daily activities.
- **Grade 2; Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Grade 3; Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term “severe” does not necessarily equate to “serious”.

8.6.1.3 RELATIONSHIP TO STUDY VACCINE OR PROCEDURE

All adverse events (AEs) must have their relationship to study vaccine (or a procedure) assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.6.1.4 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or

- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.6.1.5 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

POTENTIAL IMMUNE-MEDIATED MEDICAL CONDITIONS (PIMMC)

PIMMC is a subset of AEs i.e., Adverse Events of Special Interest (AESI) that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as PIMMCs include, but are not limited to, those listed in Table 5 below. The investigator will exercise their best medical and scientific judgment in deciding whether other diseases have an autoimmune origin and should refer to the investigational brochure. In addition, the study team will use the Brighton Collaboration Guidelines on AESI Case Definitions as provided in the website (https://brightoncollaboration.us/category/pubs-tools/case-definitions/). This list is based on the Medical Dictionary for Regulatory Activities (MedDRA), Version 24.1 and may be updated during the trial conduct.

Table 5. List of Potential Immune-Mediated Medical Conditions

Neuroinflammatory Disorders	Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy); Optic neuritis; Multiple sclerosis; Transverse myelitis; Guillain-Barre syndrome, including Miller Fisher syndrome and other variants; Acute disseminated encephalomyelitis, including site specific variants (e.g. encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis, cerebellitis); Myasthenia gravis, including Lambert- Eaton myasthenic syndrome; Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy); Narcolepsy
Musculoskeletal Disorders	Systemic lupus erythematosus; Scleroderma, including diffuse systemic form and CREST syndrome; Systemic sclerosis; Dermatomyositis; Polymyositis; Antisynthetase syndrome; Rheumatoid arthritis; Juvenile chronic arthritis, (including Still's disease); Polymyalgia rheumatica; Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis; Psoriatic arthropathy; Relapsing polychondritis; Mixed connective tissue disease
Skin Disorders	Psoriasis; Vitiligo; Erythema nodosum; Autoimmune bullous skin diseases (including pemphigus, pemphigoid and Dermatitis herpetiformis); Cutaneous

	lupus erythematosus; Alopecia areata; Lichen planus; Sweet's syndrome; Morphoea
Liver Disorders	Autoimmune hepatitis; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune cholangitis
Gastrointestinal Disorders	Crohn's disease; Ulcerative colitis; Ulcerative proctitis; Celiac disease
Metabolic Disorders	Autoimmune thyroiditis (including Hashimoto thyroiditis); Grave's or Basedow's disease; Diabetes mellitus type I; Addison's disease
Vasculitides	Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis; Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.
Other	Autoimmune hemolytic anemia; Autoimmune thrombocytopenia; Antiphospholipid syndrome; Pernicious anemia; Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis); Uveitis; Autoimmune myocarditis/cardiomyopathy; Sarcoidosis; Stevens-Johnson syndrome; Sjogren's syndrome; Idiopathic pulmonary fibrosis; Goodpasture's syndrome; Raynaud's phenomenon

COVID-19 ILLNESS

Participants will be monitored for signs of COVID-19 compatible illness throughout the study (Day -30 to Day 365). If a COVID-19 event of special interest (Table 8) occurs than a COVID-19 Report Form will be completed and expedited safety reporting timelines (e.g., SAE) will be followed as applicable.

Table 6: Adverse Events of Special Interest Relevant to COVID-19

Body System	**Diagnoses**[a]
Immunologic	Enhanced disease following immunization, cytokine release syndrome related to COVID-19[b], Multisystem inflammatory syndrome in children (MIS-C)
Respiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia

	• Myocarditis, pericarditis
Hematologic	Coagulation disorder • Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Hemorrhagic disease • Thrombotic complications
Renal	Acute kidney injury
Gastrointestinal	Liver injury
Neurologic	Guillain-Barré Syndrome, anosmia, ageusia, meningoencephalitis
Dermatologic	Chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme

When there is enough evidence to make any of the above diagnoses, the AE must be reported as an AESI and must follow reporting rules of an SAE.

8.6.2 ADVERSE EVENTS REPORTING

8.6.2.1 SOLICITED ADVERSE EVENTS REPORTING

Participants will remain in clinic for 30-60 min and be monitored for immediate reactogenicity using the parameters for local and systemic reactogenicity (tables 7 and 8 below). All participants will self-monitor (daily) solicited AEs for 7 days after vaccination. Solicited injection site and systemic reactions (tables 7 and 8) will be collected with FDA toxicity scoring applied. In the case when there are not symptoms then a grade of 0 will be applied. Subjects will be counselled to seek an immediate unscheduled visit if they record any reactogenicity that would appear to be a grade 3 or greater. Should a solicited adverse event exceed the 7 day period beyond vaccination than the event will be collected as an unsolicited adverse event, with the start date consistent with the time of the reactogenicity reporting but with standard AE clinical grading applied to the Adverse event classification. This allows the event to ensure a time to resolution is recorded.

Table 7: FDA Toxicity Table (Local Reactogenicity)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING (report as SAE)
Injection Site Pain or Tenderness	Discomfort but does not limit use of limb	Interferes with activity **OR** repeated use of non-narcotic pain relief medication.	Prevents daily activity **OR** use of narcotic pain reliever	ER visit or Hospitalized
Injection Site Erythema or Redness *Adult*	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis, or exfoliative dermatitis

*≤ 15 years of age**	≤ 2.5 cm in diameter	> 2.5 cm in diameter with <50% surface area of the extremity segment involved	≥ 50% surface area of the extremity segment involved **OR** ulceration, infection, phlebitis, abscess or drainage	
Injection Site Induration or swelling	2.5 - 5 cm **AND** does not interfere with normal activity	5.1- 10 cm **OR** interferes with normal activity	> 10 cm **OR** prevents daily activity	Necrosis
*≤ 15 years of age**	≤ 2.5 cm in diameter	> 2.5 cm in diameter with <50% surface area of the extremity segment involved	≥ 50% surface area of the extremity segment involved **OR** ulceration, infection, phlebitis, abscess or drainage	
Injection Site Pruritus*	Itching localized to the injection site	Itching beyond the injection site that is not generalized	Generalized itching causing inability to perform usual social & functional activities	NA

*DAIDS definition

Table 8: FDA Toxicity Table (Systemic Reactogenicity)

SYSTEMIC (GENERAL)	MILD (GRADE 1)	MODERATE (GRADE 2)	SEVERE (GRADE 3)	POTENTIALLY LIFE THREATENING (GRADE 4) (report as SAE)
Fever* ^{0}C	38.0-38.4	38.5-38.9	39.0-40.0	>40
Nausea/vomiting**	No interference with activity **OR** 1 – 2 episodes/24 hours	Some interference with activity **OR** > 2 episodes/24 hours	Prevents daily activity **OR** requires outpatient IV hydration	ER visit or hospitalization
Diarrhea**	2 – 3 loose stools	4 – 5 loose stools	6 or more watery stools **OR** requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Some interference with activity **OR** repeated use of non-narcotic pain reliever > 24 hours or	Prevents daily activity **OR** use of narcotic pain reliever	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization

*No recent hot or cold beverages or smoking

** Assessment is **in addition** to baseline clinical status

Individual Paper Diary Cards will be given to trial participants for the recording of daily safety information. Participants will also be provided with rulers for measuring the size of injection site reactions, and standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study nurses and clinicians will instruct participants on how to correctly use these tools. In case of an illiterate participant, the study team will arrange for assistance to the participant through a family member. On return to clinic (day 7, Visit 3), the Investigator or an authorized designee will interview the participants about the information recorded in the Diary Cards and will attempt to clarify anything that is not clear before data entry with assignment of a final FDA toxicity grade to each event. In the case when there are not symptoms then a grade of 0 will be applied.

8.6.2.2 UNSOLICITED ADVERSE EVENT REPORTING

All Adverse Events (AE) will be followed through 28 after vaccination, all Treatment Emergent Adverse Events (TEAE) through 85 days after vaccination and all AESI and SAEs will be followed until end of study. Adverse Events of Special Interest (AESIs) include COVID-19 specific complications (Table 6) and potential immune mediated medical conditions (PIMMC; Table 5). Adverse Events that occur in the above timeframes indicated will be followed until resolution, new stable condition or study completion. Anything that requires treatment beyond what the study sites can provide will be referred to an appropriate medical facility, with appropriate study staff continue to monitor. Outcomes of any AE reported during the study will be assessed as:

- Recovered/resolved
- Not recovered/not resolved
- Recovering/resolving
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

Authority reporting will follow country requires for adverse events. All sites will be notified of significant adverse events at the study level that require country level reporting, regardless of the country where the event occurred.

8.6.2.3 SERIOUS ADVERSE EVENT AND ADVERSE EVENTS OF SPECIAL INTEREST REPORTING

The investigator will promptly report all SAEs to the Sponsor and designee responsible for safety reporting in accordance with the procedures detailed in this protocol. The clinical trial Sponsor has a legal responsibility to promptly notify the country competent regulatory authority as per local regulations about the safety of a product under clinical investigation. VIBRI is also responsible for reporting events to the study's DSMB and disseminating information to all investigators in the appropriate format for reporting to local Ethics Review Committees (ERC) and Regulatory Authorities (RA), as appropriate. Prompt notification of SAEs by the investigator to the Sponsor and designee is essential so that legal obligations and ethical responsibilities towards the safety of other participants are met. The purpose of the report is to fulfill specific regulatory and GCP requirements, regarding the product under investigation. Table 9 below describes the timelines for submission of SAEs and other events reports to the sponsor.

Suspected Unexpected Serious Adverse Reactions (SUSAR) are reportable to Ethics and Regulatory Authorities similar to SAEs.

Table 9: Timeframes for Submitting Serious Adverse Events and Other Event Reports to the Sponsor and Regulatory Authorities

Type of Event	Initial Reports		Emerging Relevant Information		Follow-Up Report	
	Timeframe*	Documents	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours	SAE report	24 hours	SAE report	7 days	SAE report
AESI	24 hours	SAE report	24 hours	SAE report	7 days	SAE report
SUSAR	24 hours	SAE report	24 hours	SAE report	7 days	SAE report
Pregnancy	24 hours	Pregnancy report	48 hours	Pregnancy report	24 hours of outcome	Infant report

Once an investigator becomes aware/confirms that a SAE has occurred in a study participant, the investigator (or designate) must complete the information in the SAE report as thoroughly as possible with all available details of the event, within 24 hours. Even if the investigator does not have all information regarding a SAE, the report must be completed and reported within 24 hours. Once additional relevant information is received, the report should be updated within 7 days of receipt of relevant information. The investigator will always provide an assessment of causality at the time of the initial report. The investigator is required to proactively follow each participant and provide additional relevant information on the participant's condition to the Sponsor and/or designee responsible for medical monitoring and safety reporting.

Once onset of an AESI is diagnosed in a study participant, the investigator (or designate) must complete the information on the AESI report within 24 hours after awareness of the diagnosis. AESI will be reported within 24 hours. Updates to reported AESIs will follow SAE reporting criteria.

An SUSAR that occurs in the trial requires reporting to each investigator who will then file it within the Investigator Study File and will notify the IRB/IEC and the country regulatory authority within 7 calendar days.

The Sponsor may request that the investigator performs or arranges the conduct of additional clinical examinations/tests and/or evaluations, within the limits of available care, to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obliged to assist. If a participant dies during participation in the study or during a recognized follow-up period, the DSMB, Sponsor, and IRB will be provided with any available post-mortem findings.

Annual safety reporting (or more frequent if required) will be provided to ethics and regulatory authorities per requirements.

8.6.2 REPORTING OF PREGNANCY

Pregnant women are not eligible to participate in the study and females of childbearing potential must agree to use an effective contraceptive method during a period starting 4 weeks prior to through 12 weeks following vaccination. However, a participant could potentially become pregnant during her participation. If a pregnancy occurs during study participation:

- When pregnancy exposure is reported following booster vaccination, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit to the safety database and per ethics and regulatory authorities within the designated regulatory reporting period.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed through delivery/termination of pregnancy with information on the participant and the neonate. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

The investigator, or his designee, will record pregnancy information on the Pregnancy Notification Report Form and submit it to the respective ethics committees and country regulatory authorities. The Sponsor will review all pregnancy reports as will the medical monitor. Follow up reports regarding the outcome of the pregnancy will be submitted once obtained.

8.6.3.3 REPORTING EVENTS TO PARTICIPANTS

When new pertinent information becomes available, informed consent will be updated and participants reconsented.

8.6.5 UNANTICIPATED PROBLEMS REQUIRING ETHICS COMMITTEE REPORTING

8.6.5.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP) AND REPORTING

The unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the ERC-approved research protocol and

informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems include problems that are not specifically described in the protocol that affect subjects or personnel involved in trial conduct. Events that are identified as significant protocol deviations or safety issues will be assessed by investigators and with sponsor oversight for appropriate ethics committee reporting on a routine basis and as per ethics requirements within each country. The seriousness of the event will be included and if additional important data become available at a later date then ethics committees will be updated accordingly. For example, misplacing a participant's study records containing identifiable private information results in the risk of breach of confidentiality. Another example would be administering the wrong agent to a participant at one-time point in a series of vaccinations. Risks to others must also be reported. Appropriate supporting documents should be submitted with the unanticipated problem report.

All non-serious unanticipated problems (events not involving risk to participants or others) will be reported in the continuing review report to the respective ethics committees for the study sites as per regulatory requirements.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null and alternative hypothesis for the primary endpoints:

H_0 (Safety): There is no expected difference in % solicited adverse events (AEs) across the three vaccine platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.
H_1 (Safety): There is an expected difference in % solicited adverse events (AEs) across the three vaccine platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_0 (Safety): There is no expected difference in SAE rate attributed to vaccine across the three vaccine platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.
H_1 (Safety): There is an expected difference in SAE rate attributed to vaccine across the three vaccine platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_0 (Immune Response IgG): Among participants with HIV infection there is no expected difference in the GMT or GMFR response by ELISA between the 2 vaccine treatment groups at Day 28 for any one platform or across all platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.
H_1 (Immune Response IgG): Among participants with HIV infection there is an expected difference in the GMT or GMFR response by ELISA between the 2 vaccine treatment groups at Day 28 for any one platform or across all platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_0 (Immune Response Neutralization): Among participants with HIV infection there is no expected difference in the neutralization titre response (absolute or GMFR) between the 2 vaccine treatment groups at Day 28 for any one platform or across all platforms after boosting with either Ad26.COV2S1vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.
H_1 (Immune Response Neutralization): Among participants with HIV infection there is an expected difference in the GMT response by neutralization titre response (absolute or GMFR) between the 2 vaccine treatment groups at Day 28 for any one platform or across all platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_0 (Immune Responses compared to immune competent): Among participants with HIV infection there is an expected lower immune response over time (IgG ELISA and neutralization titres) when compared

to HIV (-) participants for any one platform or across all platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_1 (Immune Responses compared to immune competent): Among participants with HIV infection there is not an expected lower immune response over time (IgG ELISA and neutralization titres) when compared to HIV (-) participants for any one platform or across all platforms after boosting with either Ad26.COV2S1 vs NVX-CoV2373 for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_0 (SARS-CoV-2 breakthrough infections): There is no expected difference in breakthrough SARS-COV2 infections (AEs) after boosting with either Ad26.COV2S1 vs NVX-CoV2373 (across primary vaccine platforms) and for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

H_1 (SARS-CoV-2 breakthrough infections): There is an expected difference in breakthrough SARS-COV2 infections (AEs) after boosting with either Ad26.COV2S1 vs NVX-CoV2373 (across primary vaccine platforms) and for adults and Novavax NVX-CoV2373 vs mRNA (Moderna mRNA-1273 or Pfizer/BNT) vaccines for adolescents.

Sequentially rejective procedures will be used within secondary objectives and will be ordered in the Statistical Analysis Plan in the following general hierarchy. Within each of the general hierarchy endpoints will be tested by order according to their relative importance. Within an objective, if more than one endpoint is included, a Holm procedure (also known as a stepdown Bonferroni procedure) will be used to account for multiple testing. The importance order for secondary objectives and Holm procedure will be described in the statistical analysis plan (SAP). Further details of the planned statistical analyses, methods, and data conventions will be described in the SAP.

9.2 STATISTICAL ANALYSES

The statistical analysis will be conducted following the principles as specified in the International Conference on Harmonization (ICH) Topic E9 (ICH, 1998). There will be 3 interim analyses with database freeze and a final statistical analysis performed after database lock.

All data will be collected and verified prior to analysis. Detailed statistical procedures, listings, table shells, and figures will be provided in a statistical analysis plan (SAP). The SAP will be finalized before study temporary database lock for interim analysis and will be signed off by the Sponsor prior to conducting any analyses.

The following key statistical components and a detailed description will be documented in the SAP:

- Primary and secondary endpoints and how they will be measured
- Statistical methods and tests that will be used to analyze the endpoints

- Strategy that will be used if the statistical test assumptions are not satisfied e.g., log transformation of IgG titres to render normality assumptions.
- Indication of whether the comparisons will be using one-tailed or two-tailed tests (with justification of the choice) and the level of significance to be used
- Identification of whether any adjustments to the significance level or the overall p-value will be made to account for any planned or unplanned subgroup analyses or multiple testing.
- Specification of potential adjusted analyses and a statement with which covariates or factors will be included. This will include comparison between the 2 booster vaccines and interaction with HIV status
- Planned exploratory analyses and justification of their importance

The number of participants enrolled, randomized, vaccinated, completed, or withdrawn will be summarized. Reasons for withdrawal, when known, will be provided. Demographic data will be summarized by descriptive statistics and will include total number of observations (n), mean, standard deviation (SD) or median and interquartile range as appropriate for continuous variables, and number and percentages for dichotomous variables.

The safety analysis set will consist of all randomized participants who receive study vaccine and have any safety data available. Participants will be classified according to the actual vaccine received. Safety will include a) reactogenicity (solicited) daily for 7 days following vaccination; b) adverse events (unsolicited) through 28 days following vaccination; c) TEAE through 84 days following vaccination and c) AESI and SAEs through end of study.

The intent-to-treat analysis set will consist of all randomized participants. Participants will be classified according to study group. Participant's disposition, demographics, and medical history will be summarized on the analysis set.

The immunogenicity analysis set will consist of all participants in the intent-to-treat analysis set who receive study vaccine, have a baseline and at least 1 post-vaccination sample for which valid results were reported for the test being analysed, and did not receive any COVID-19 vaccine or monoclonal antibody outside of the study. Participants will be classified as randomized.

Statistical analysis will be performed using STATA version 16 or later and R software. Continuous variables will be summarized using the mean and standard deviation or median or median and interquartile range as appropriate. Categorical variables will be summarized using frequency counts and percentages, as well as 2-sided 95% confidence interval (CI) for proportions computed using the Clopper-Pearson method tests of associations using a Chi-square or the Fishers exact test as appropriate.

Immunogenicity endpoints (GMT, GMFR) will be summarized by age groups (12-17, 18-44, 45-64) and across age groups, by country (within age groups), by primary platform and by boosting vaccine. Additional descriptive analysis by CD4 counts and key co-morbid health diagnoses will be performed to

assess if any participant who progresses to a more severe immunocompromised status has reduced immunity compared to counterparts. Reporting will be at country level and in aggregate. Serum and mucosal immunogenicity endpoints will be summarized by treatment group at each time point collected, relative to baseline and relative to pre-boost values and will include the GMTs with 95% CIs and GMFRs with 95% CIs. Similar reporting will occur for neutralization results using pseudo neutralization readouts. All assays will be standardized using WHO (or similar) standards. For immunogenicity analysis, it is assumed that the natural log of the data is normally distributed. All statistical tests will be 2-sided at 5% significance level.

The SARS-CoV-2 breakthrough disease analysis set will consist of all participants in the intent-to-treat analysis who received at least one dose of study vaccine and contributed data on SARS-CoV-2 symptoms following Day 28. The analysis will report out SARS-CoV2 cases a) by booster vaccine (all cases); b) by primary platform series (all cases); c) by booster within primary platform series (all cases); d) by severity (mild, moderate, severe) (both by vaccine booster and by primary platform series for each vaccine booster); e) divergence of Kaplan Meier (KM) estimates for SARS-CoV-2 severe cases (including death); f) by VOC in moderate and severe cases by vaccine booster and by primary vaccine platform. The vaccine efficacy post booster will be compared between the two arms as an exploratory objective as the study is not powered to test these strategies. The SARS-CoV-2 event rates (and severity) will continue to be collected through end of study and descriptive analyses will be reported (including KM curves).

A longitudinal analysis of safety and immunogenicity will be conducted at different timepoints during the study including from baseline, D28, D85, 6mo, 12mo to end of the study.

Interim analyses

There will be 3 interim analysis time points by vaccine platform: a) 28 days following booster vaccination in adults/adolescents (safety and immunogenicity); b) 6 months after adult/adolescent booster vaccination; c) 12 months after booster vaccination for all subjects (safety, immunogenicity and SARS-CoV-2 breakthrough infections). The interim analyses will be at the treatment level only and blinding will remain at the individual level, site level and for all operational teams and sponsor. The final database lock and analysis will occur after all adult participants have completed the long term follow up (15-18 months) and adolescents have completed 12 months of follow up. Both sponsor and DSMB will have interim analyses available for decision making.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local ERC/IRB requirements and/or national regulations and directives.

Before the inclusion of the first participant, this protocol, the informed consent form (ICF), and other written information to be provided to participants will be approved by, and/or receive favorable opinion from, the appropriate ERCs or IRBs. In accordance with Good Clinical Practice (GCP) and local regulations, each Investigator and/or the Sponsor are responsible for obtaining this approval and/or favorable opinion before the start of the study. If the protocol is subsequently amended, approval will be re-obtained for each substantial amendment from the relevant ERC/IRB depending on the nature of the amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, will be forwarded by the Investigator to the Sponsor.

According to the WHO, National Regulatory Authorities and National Ethics Committees from across Africa agreed to combine their expertise to expedite clinical trial review and approvals for new multinational preventive, diagnostic and therapeutic interventions to the COVID-19 pandemic. However, joint reviews are based on voluntary cooperation between the national regulatory authorities and ethics committees. Each country is solely responsible for granting regulatory approval. The agreement was reached during a virtual meeting convened by the World Health Organization (WHO) on 1 April 2020 under the platform of the African Vaccines Regulatory Forum (AVAREF), one of the Continental Technical Committees of the African Medicines Regulatory Harmonization Initiative.

10.1.1 KENYA ETHICS AND REGULATORY APPROVAL

The Key ethics and regulatory bodies mandated to regulate medical research including clinical trials in Kenya are the National Commission for Science, Technology and Innovation (NACOSTI) and the Kenya Pharmacy and Poisons Board (KPPB). NACOSTI gives accreditation to Ethics Review Committees including the Amref Scientific and Ethics Review Committee (ESRC). Before commencement of the study, the protocol, the informed consent form (ICF), participant recruitment procedures, and any other written information to be provided to participants must be approved by, and/or receive favorable opinion from, the Amref ESRC and the Kenya Pharmacy and Poisons Board, Expert Committee on Clinical Trials. In accordance with Good Clinical Practice (GCP) and local regulations, the Principal Investigator and/or the Sponsor will be responsible for obtaining ethical and regulatory approval and/or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be obtained for each amendment. All amendments (e.g., those that affect the conduct of the study or the safety of participants) require Amref ESRC approval, and must also be forwarded to regulatory authority i.e., the Kenya Pharmacy and Poisons Board. In Kenya, ethical approval is required prior to approval from the regulatory

authorities. The ethical approval process at Amref ESRC will occur in parallel with the Kenya Pharmacy and Poisons Board which takes about 1 month. Before the investigational product can be shipped to the investigational site, the pharmacy and poisons board issues a permit after approval of the protocol and study documents. Please note that for Covid-19 protocols, the review process will be expedited. Approval will also be sought in parallel from the County Ministry of Health and this takes a few days. The Amref ESRC and KPPB charge a standard fee for their review and approvals.

10.1.2 RWANDA ETHICS AND REGULATORY APPROVAL

The key ethics and regulatory bodies mandated to regulate medical research including Clinical Trials in Rwanda are the Rwanda National Ethics committee (RNEC) which takes control on ethical aspects of research projects intended to be conducted on human participants, the National Health Research Committee (NHRC) which aligns the research intended to be conducted in the country with the national health research agenda. The Rwanda Food and Drug Administration (RFDA) is the National Medicine Regulatory Authority that provides regulatory approvals for clinical trials. The first step involves submission to the Rwanda Biomedical Center (RBC) for the protocol and investigator brochure (IB). Approval takes/feedback takes about 5 days after which submission is made to the National Health Research Committee (NHRC) for the protocol and IB. The NHRC approval takes 2-4 weeks. This is followed by submission to the RNEC which meets monthly. Comments on the application are sent out within 2 weeks of after the RNEC meeting. It takes about 2 months to obtain approvals at this level. After RNEC approval, submission is made to the RFDA, and approval is obtained within 60 days. The RNEC and RFDA charge a standard fee for their review and approvals.

10.1.3 DEMOCRATIC REPUBLIC OF CONGO ETHICS AND REGULATORY APPROVAL

The Directorate of Pharmacy and Medicine (Direction de la Pharmacie et du Medicament (DPM) of the Ministry of Health (Ministèere de la Santée) is the regulatory authority responsible for allowing clinical trials, as well as authorizing and controlling drug imports and exports, in the Democratic Republic of the Congo (DRC). In addition, an ethics committee (EC) must review the scientific validity and ethical acceptability of any research proposal involving human participants.

The DPM is comprised of six (6) divisions including the Drug Management Division; the Pharmacy Division; the Division of Narcotic, Psychotropic and Dangerous Substances; the Division of Veterinary, Plant Protection, Cosmetic, and Dietary Products; the Division of Insurance and Quality Control of Medicines; and the Division for the Promotion of Medicinal Plants. The Pharmacy Division of the DPM is in charge of pharmaceutical inspection and legislation. The Pharmacy Division includes two 2 offices: inspection and control of pharmacy practice, and legislation, statistics, and archives. Pharmaceutical inspection focuses on best practices, including Good Manufacturing Practices (GMP) for manufacturing laboratories and drug production units, and Good Clinical Practices (GCP) for developing and conducting clinical trials for new drugs. The Pharmacy Division's clinical trial responsibilities are carried out in collaboration with the National Ethics Committee (EC), the National Committee of Health Ethics (Comité National d'Éthique de la Santé (CNES)). CNES activities include regulatory follow up and inspecting clinical trial sites. The National

Ethics Committee must approve the protocol, budget and investigator brochure. They meet monthly and it takes about 4 weeks to get approval. The EC approval is a precondition for RA review. The RA review takes about 1 week to get approval in the context of COVID-19.

The DPM's Division of Insurance and Quality Control of Medicines is responsible for pharmacovigilance and has four offices. The DRC's National System of Pharmacovigilance, implemented by the DPM, aims to identify as early as possible all the adverse effects of health products, especially those that are serious and unexpected. It includes the DPM's National Pharmacovigilance Commission, which evaluates the risks incurred by participants in a clinical trial and advises the DPM on the trial's continuation or discontinuation. In addition, the National Pharmacovigilance Center, established within the University of Kinshasa's Unit of Clinical Pharmacology and Pharmacovigilance, is responsible for collecting information from manufacturers, health professionals, and other individuals on the adverse effects of health products; establishing accountability; and assessing the relative risk. For their review and approvals, the EC charges a fee of 2% of non-investment costs calculated from the study budget and RA charges a standard annual fee for none registered product applications and a very minimal fee for trials based on registered products.

10.2 PROTOCOL AMENDMENTS

Any amendments to this protocol must be discussed and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version.

All substantial amendments (e.g., those that affect the conduct of the study or the safety of participants) require Ethics Review Committee (ERC/IRB) approval and must also be forwarded to regulatory authorities. An administrative amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the participants' safety. The ERCs/IRBs need only to be notified about administrative changes. The Investigator is responsible for ensuring that changes to an approved study, during the period for which ERC approval has already been given, are not initiated without ERC review and approval, except to eliminate apparent immediate hazards to participants.

10.3 REPORTING REQUIREMENTS

10.3.1 CONTINUING REVIEW REPORTING

The PI or designee will be responsible for submitting the required continuing review report and supporting documentation to the respective study site's ERC and regulatory authorities, allowing sufficient time for review and continuation determination prior to the established continuing review date.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The Sponsor will comply with

country-specific regulatory requirements relating to safety reporting to the regulatory authority, ERC and investigators.

10.3.2 PROTOCOL DEVIATION REPORTING

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. A major deviation is a non-compliance that significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and integrity of the study data. A major deviation can include nonadherence to regulatory authority including ICH E6(R2) guidelines.

Major protocol deviations will be reported by email and/or phone to the respective ERC/IRB and regulatory authority according to respective country guidelines. All deviations will be summarized in the continuing review reports that are submitted. A copy of continuing review report will be provided to the Sponsor for acknowledgment. The Principal Investigator or designee is responsible reporting the major and minor deviations to the Sponsor and the ERCs appropriately.

Sponsor and study sites will conduct regular Protocol deviation review meetings during the study with final classification agreed upon.

Any suspensions (to include continuing review lapses), clinical holds (voluntary or involuntary), or terminations of this research by an ERC, the institution, the Sponsor, or regulatory agencies will be promptly reported to the Sponsor, ERC and authorities.

10.3.3 REPORTING OF INSPECTIONS OR AUDITS

Knowledge of any pending compliance inspections/visits by a government agency concerning clinical investigation or research, the issuance of Inspection Reports, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to the ERC and Sponsor by phone, email or facsimile.

10.4 INFORMED CONSENT PROCESS

Consent forms describing in detail the study agent, study procedures, and risks and benefits are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study products.

10.4.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS

Consent forms describing in detail the study agent, study procedures, and risks and benefits are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study products.

Test of Understanding (TOU)

The TOU is a short assessment of the participants or parent/guardian of the potential participant's understanding of key aspects of the study. The test will help the study staff to determine how well the participant or parent/guardian understands the study and their requirements for participation in the study. The participant or parent/guardian must pass the TOU, indicating that he or she understands the purpose of, and procedures required for the study, after reading the informed consent and after the investigator or designee has provided detailed information on the study and has answered the questions of participant or the parent/guardian. The participant or parent/guardian must subsequently sign the ICF, indicating that he or she is willing to allow their child to participate in the study. If a participant or a parent/guardian fails to achieve the passing score on an attempt, further information and counselling will be provided to the participant or parent/guardian by a study team member. The participant or parent/guardian is allowed to retake the test twice to achieve the passing score (≥90%) required for participation of their child in the study. If the participant or parent/guardian fails to achieve the passing score on the third attempt they will not be able to re-take the test again, and their child will not be allowed to participate in the study. Any participant or parent/guardian of a potential participant not capable of understanding the key aspects of the study, and their requirements for participation, should not be allowed to enroll in the study.

10.5 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor(s). This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, 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 unauthorized third party without prior written approval of the Sponsor. The study monitor, other authorized representatives of the Sponsor, ERCs/IRBs and regulatory agencies may inspect all documents and records required to be maintained by the investigator.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location.

10.6 FUTURE USE OF STORED SPECIMENS AND DATA

Left over biological samples and use of data, any unused part of the serum or other biological samples collected for this study may be retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results. After the end of the trial, any unused part of the serum or respiratory samples will be securely stored at the VIBRI, CEPI CL Lab Network or Contract Research Organization (CRO) up to 10 years. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the trial results. Participants will be asked to consent for the future use of these specimens beyond the scope of the testing outlined in this protocol, but consent for future use will not

be required for participation in this study. Participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests not related to trial objectives. If they refuse permission, the samples will not be used for any testing other than that directly related to this trial. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. Genetics are not evaluated in this study.

10.7 KEY ROLES AND STUDY GOVERNANCE

The study will have a Joint Steering Committee (JSC) composed of representative of the funding agency and the sponsor. The JSC will monitor progress of the study. The protocol implementation will be overseen by Trial Management Committee (TMC) composed of the Study Chairman, Site Study Coordinators, Project Managers, Data Managers, Laboratory Leads. The TMC will oversee implementation of the protocol. Data and Safety Monitoring Board (DSMB) will be responsible for safeguarding the interests of the trial participants and to monitor the data collected in the trial. Specific roles and responsibilities of the DSMB will be outlined in the DSMB Charter. The sponsor and principal investigator will agree, in writing prior to the start of the study, to the charter of the DSMB. The DSMB will conduct meetings on a quarterly basis but could also have ad hoc meetings.

10.8 SAFETY OVERSIGHT

The Medical Monitor or their approved alternate are required to review all unanticipated problems involving risks to participants or others, and serious adverse event (SAE) reports, in a timely manner as described in the safety monitoring plan. Scheduled reviews with the sponsor's medical representative will occur. The Medical monitor is responsible for observing for study pauses and will declare when a study pause rule has been met. They are responsible for ensuring needed safety evaluations are available to the DSMB. The medical monitor must complete a review of the final assessment of any AE related to IP and provide summary assessments to the sponsor on pre-arranged frequency as outlined in the safety monitoring plan. Medical monitors have the authority to pause enrollment or vaccination, trigger further investigation at a site or take additional steps necessary to protect the safety and well-being of research participants.

10.9 CLINICAL MONITORING

Appropriate training of the protocol and all associated activities (e.g. data entry, data cleaning, pharmacy procedures, laboratory procedures, documentation practices, etc). is the responsibility of the sponsor and any designee. Site clinical monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). A separate clinical monitoring plan (CMP) will be prepared by the CRO for the study. The primary objectives of the monitors during the on-site and remote visits will be to ensure the study is being conducted according to the protocol, SOPs are adhered to, the site is following GCP, all regulatory requirements are being met and appropriately documented. Monitors will assess the overall quality and completeness of the data, examine source documents, interview investigators and coordinators, and confirm that the clinical centre has complied with the requirements of the protocol. The monitors will verify that all consents have been obtained and adverse events were documented in the correct format and are consistent with protocol definition.

The monitors will review the source documents as needed, to determine whether the data reported in the electronic case report forms are complete and accurate. Monitoring will involve periodic independent review of core trial processes and documents. Monitoring will be intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action if necessary. In case of an audit, the processes reviewed will relate to participant enrolment, consent, eligibility, and allocation to study groups; adherence to trial interventions and policies to protect participants, including reporting of harms and completeness, accuracy, and timeliness of data collection. In addition, monitoring will verify adherence to applicable policies such as the International Conference on Harmonisation *Good Clinical Practice* and regulatory agency guidelines.

In this study, the ethics review committees, regulatory authorities and the sponsor may conduct auditing of source documents at any of the enrolling sites.

10.10 QUALITY ASSURANCE AND QUALITY CONTROL

The study sites have SOPs in place for quality management to ensure compliance with ICH-GCP, the protocol, ethical standards, and regulatory requirements. Having the highest quality data and studies are essential aspects of vaccine development. To compliance with GCP, it may be necessary for the Sponsor to conduct a site audit. This may occur at any time from start of the study to the period after the conclusion of the study. The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. When an investigator will provide direct access to source data/documents including the following:

- ERC/IRB approval
- Vaccine accountability
- Approved study protocol and amendments

- Informed consent of the participants
- Medical records and other source documents supportive of CRF data
- Reports to the ERC/IRB, and the Sponsor
- Record retention

The study sites have SOPs for quality management that include staff training methods, product accountability records, specimen tracking logs, questionnaires, audio or video recordings. The Quality Control (QC) procedures will be implemented beginning with the source documents, data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site(s) for clarification or resolution. Following written SOPs, the monitors will verify that the clinical trial is conducted, data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

10.11 DATA HANDLING AND RECORD KEEPING

10.11.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Principal Investigator (PI). The PI is responsible for assuring that the data collected is complete, legible, attributable, accurate, and recorded in a timely manner. Data recorded in the eCRF should be consistent with the data recorded on the source documents. All source documents and laboratory reports must be reviewed by the site team, who will ensure that they are accurate and complete.

SOURCE DATA

All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH E6 section 1.51].

SOURCE DOCUMENT

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participant diaries, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial are considered Source Documents. [ICH E6 section 1.52]

DATA CAPTURE METHOD

Clinical data recorded in source documents, should be completed in a neat, legible manner to ensure accurate interpretation of data in accordance with ALCOA principles of Good Documentation Practice. Source documentation supporting the CRF data should document the dates and details of study procedures, AEs and participant status. The PI will ensure that all information in the CRFs and all source

documents that support the data collected from each participant are maintained in a secure area and treated as confidential material.

The clinical data in the source documents (including AEs, concomitant medications, and expected adverse reactions data) will be entered by remote data entry into an EDC system by trained and qualified study staff. Data reported in the CRF derived from source documents should be consistent with the source documents, and it is the PI's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's CRF and any supporting documentation. The CRF for the study will be developed and provided by the Sponsor.

Additionally, a description of this clinical trial will be available on https://www.ClinicalTrials.gov and the Pan African Clinical Trial Registry (PACTR) at https://pactr.samrc.ac.za. The clinical trial registries will not identify any individual participants and will include a summary of the results.

DATA MANAGEMENT

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

DATA STORAGE

All study documentation containing personal information relating to study participants like consent forms and other documents that might link participant ID with other participant personally identifiable information (PII) will be kept in a secure locked area with limited access at the study sites. Such documentation will only be made available to authorized personnel. These study documents will be made available to the investigators, clinical personnel who require this information to treat the participants and the above-mentioned personnel for inspection or auditing reasons. In addition, access to participants' medical records will be granted to representatives of the Sponsor, regulatory agencies, and ethics committees for the purpose of validating data.

10.11.2 STUDY RECORDS RETENTION AND DISPOSAL

Study documents will be retained for the duration required by the Sponsor, applicable local regulations, and in accordance with GCP standards, in a safe and secure facility. No records will be destroyed without the written consent of the Sponsor. Upon study completion, all records will be stored safely at the respective study sites archiving facilities or at a secure contracted storage facility. If storage at an alternative facility is considered, this will be documented, and the documentation will be filed in the study's regulatory file. Should longer storage be recommended by the Sponsor or relevant authorities, the site will contact the reviewing ERC/IRBs for consideration and approval. Study files can be stored either as paper or digitally. Digitization, if done, will consist of the scanning of all paper records according to site SOPs to ensure accurate and complete representation of the same. This may be done by the site staff of a contracted third-party. All digitized records will be maintained on a secure, password protected computer system with access limited to those with access to study as previously listed in this protocol as well as VIBRI's archivist(s) and IT personnel who will maintain the database. Upon completion of

digitization of study records, and receipt of a Sponsor's approval, paper copies may be destroyed by incineration according to site SOPs.

Paper or digitized records may be disposed of after storage duration has been met (15 years or as otherwise specified above) and with the Sponsor's written approval. Any remaining paper records will be incinerated and if digitized, the records will be securely deleted. The final disposal of any remaining paper or digitized records will be witnessed by a representative of VIBRI's regulatory affairs department and will be documented. The documentation of records disposal will be provided to the Sponsor and a copy will be stored at the Regulatory Affairs department.

10.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. The study sites have no conflict of interest to disclose.

10.13 ADDITIONAL CONSIDERATIONS

10.13.1 EXPECTED APPLICATION OF THE RESULTS

The results of this trial will add to the body of scientific knowledge on the safety and immune responses of the two COVID-19 vaccines in pediatric populations and HIV populations in Africa. *The current design is to provide a standard booster (per current guidelines) at 5-7 months from the time of completion of the primary series for adult participants and ≥5 months after the primary series for adolescent participants. The optimal booster is defined by the current guidelines. We are looking at durability of response and that can inform on if and when another booster might be needed, depending on response to heterologous boosting in this population.*

10.13.2 PUBLICATION AND DATA SHARING POLICY

This study will comply with Sponsor and CEPI policies. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The final study results will be shared with the study team, the study participants, the medical community, the study sponsor, study funder and the general public. The results will be published in peer reviewed scientific journals, abstracts, posters and symposium presentations at local and international conferences. The results will be shared with the media and through dissemination activities with relevant stakeholders including the Ministry of Health

11 ABBREVIATIONS

AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALT	Alanine aminotransferase
CBC	Complete Blood Count
CEPI	Coalition for Epidemic Preparedness Innovations
CHW	Community Health Worker
CI	Confidence Interval
CMI	Cell Mediated Immunity
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRC	Clinical Research Center
CRO	Contract Research Organization
CVD	Cardiovascular Disease
eCRF	Electronic Case Report Forms
DMP	Data Management Plan
DOD	Department of Defense
ECCT	Expert Committee on Clinical Trials (ECCT)
eCRF	Electronic Case Report Form
EDC	Electronic date capture
ELISA	Enzyme-linked immunosorbent assay
ERC	Ethics Review Committee
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FV	Field visit
GCP	Good Clinical Practice
H0	Null hypothesis
HA	Alternative hypothesis
Hb	Haemoglobin
HDSS	Health and Demographics Surveillance System
HIV	Human immunodeficiency virus
HTN	Hypertension
IB	Investigator's Brochure
IMP	Investigational Medical Product
IRB	Institutional Review Board
ICH	International Council for Harmonization
IM	Intramuscular
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PCR	Polymerase chain reaction
PI	Principal Investigator
PII	Personal identifying information
PIMMC	Potential immune mediated medical conditions
PLT	Platelet
PPB	Pharmacy and Poisons Board
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
UNIKIN	University of Kinshasa
US	United States
VE	Vaccine efficacy
VIBRI	Victoria Biomedical Research Institute
WBC	White blood count
WHO	World Health Organization

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