CLINICAL TRIAL PROTOCOL

A PHASE 2/3, OBSERVER-BLIND, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF COVISHIELD (COVID-19 VACCINE) IN HEALTHY INDIAN ADULTS

Protocol number:	ICMR/SII-COVISHIELD
Version:	5.0
Date:	06 Feb 2021
Amendment:	04
Investigational Products:	COVISHIELD (SII-ChAdOx1 nCoV-19) and Oxford/AZ-ChAdOx1 nCoV-19: a replication-deficient simian adenoviral vector expressing the spike (S) protein of SARS-CoV-2

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LIST OF ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ADE	Antibody Dependent Enhancement
AE	Adverse event
CI	Confidence interval
CLIA	Chemiluminescence Immunoassay
CMI	Cell Mediated Immunity
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Contract research organization
CTRI	Clinical trials registry of India
DCGI	Drugs controller general of India
E	Envelope protein
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme- linked Immunospot
GCP	Good Clinical Practices
GFP	Green Fluorescent Protein
GLP	Good Laboratory Practices
GMTs	Geometric mean titers
IcEv	Intercurrent Events
ICF	Informed consent form
ICMR	Indian Council of Medical Research
ICU	Intensive Care Unit
IEC	Institutional Ethics Committee
IFN-γ	Interferon-gamma
IM	Intramuscular
M	Membrane protein
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome-Coronavirus
N	Nucleocapsid protein
Nab	Neutralising Antibody
NHPs	Non-Human Primates
RT-PCR	Reverse transcription Polymerase Chain Reaction
PI	Principal Investigator
PSRT	Protocol Safety Review Team

PT	Preferred term
RBD	Receptor Binding Domain
S	Spike glycoprotein
SAE	Serious adverse event
SARS-CoV	Severe Acute Respiratory Syndrome-Coronavirus
SIIPL	Serum Institute of India Private Limited.
SOC	System Organ Class
SOP	Standard Operating Procedure
tPA	Tissue Plasminogen Activator
VP	Virus Particle
WHO	World Health Organization

PROTOCOL SUMMARY

Title	A phase 2/3, observer-blind, randomized, controlled study to determine the safety and immunogenicity of COVISHIELD (COVID-19 vaccine) in healthy Indian adults
Study No.	ICMR/SII-COVISHIELD
Phase	2/3
Study rationale	The COVID-19 epidemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Containment measures have failed to stop the spread of virus, which has reached pandemic levels. There are currently no specific treatments available against COVID-19 and accelerated vaccine development is urgently needed. Live attenuated viruses have historically been among the most immunogenic platforms available, as they have the capacity to present multiple antigens across the viral life cycle in their native conformations. However, manufacturing live-attenuated viruses requires complex containment and biosafety measures. Furthermore, live-attenuated viruses carry the risks of inadequate attenuation causing disseminated disease, particularly in immunocompromised hosts. Given that severe disease and fatal COVID-19 disproportionally affect older adults with co-morbidities, making a live- attenuated virus vaccine is a less viable option. Replication competent viral vectors could pose a similar threat for disseminated disease in the immuno-suppressed. Replication deficient vectors, however, avoid that risk while maintaining the advantages of native antigen presentation, elicitation of T cell immunity and the ability to express multiple antigens. Subunit vaccines usually require the use of adjuvants and whilst DNA and RNA vaccines can offer manufacturing advantages, they are often poorly immunogenic requiring multiple doses, which is highly undesirable in the context of a pandemic. Chimpanzee adenovirus (ChAd) vaccine vectors have been safely administered to thousands of people using a wide range of infectious

	disease targets. ChAdOx1 vectored vaccines have been given to over 320 volunteers with no safety concerns and have been shown to be highly immunogenic at single dose administration. Of relevance, a single dose of a ChAdOx1 vectored vaccine expressing full-length spike protein from another betacoronavirus (MERS-CoV) has shown to induce neutralising antibodies in recent clinical trials. ChAdOx1 nCoV-19 vaccine has been already administered in more than 500 healthy adults of 18 to 55 years in Phase 1/2 study in United Kingdom (UK). A Phase 2/3 clinical efficacy study is ongoing in approximately 10,000 individuals in UK. In addition, large Phase 3 clinical efficacy studies are ongoing in South Africa and Brazil. Also a large Phase 3 efficacy study is planned in USA. So far, no safety concerns are observed and the efficacy data from ongoing studies are awaited. COVISHIELD may also be used in these clinical efficacy studies. We will get efficacy data on huge population for this vaccine from various countries. Considering the large safety and efficacy data from these studies, we have planned this Phase 2/3 safety and immunogenicity study in Indian population for licensure in India.
Population:	1600 healthy individuals ≥ 18 years of age of which 400 will be part of immunogenicity and reactogenicity cohort
Participation Duration:	Approximately 6 months
Study duration:	Approximately 7 months: 1 month for recruitment and 6 months of follow up
Description of study vaccine (s):	**<u>Test Vaccine</u>** **COVISHIELD (SII-ChAdOx1 nCoV-19):** COVISHIELD consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2. The vaccine will be available as a ready to use liquid formulation in a 5 mL vial. **<u>Active comparator vaccine for Immunogenicity cohort</u>**

<table>
<tr><td></td><td colspan="2">Oxford/AZ-ChAdOx1 nCoV-19:
ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2.
The vaccine will be available as a ready to use liquid formulation in a vial.
<u>Comparator product for Safety cohort</u>
Placebo:
Composition of Placebo is similar to COVISHIELD except that it will not contain active ingredient (adenovirus vector ChAdOx1, containing spike protein antigens of SARS-CoV-2).
Placebo will be available as a ready to use liquid formulation in a vial.

All the study vaccines (COVISHIELD / Oxford/AZ-ChAdOx1 nCoV-19 vaccine / Placebo) will be administered intramuscularly (IM) as two doses of 0.5 ml on Day 1 and Day 29. The preferred site for injection is deltoid muscle. Each dose of 0.5 ml of COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccine contains 5 x 10^{10} VP.</td></tr>
<tr><td rowspan="7">Objectives and endpoints:</td><td>Objectives</td><td>Endpoints</td></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>To assess the safety of COVISHIELD</td><td>Occurrence of causally related serious adverse events (SAEs) throughout the study duration following vaccination</td></tr>
<tr><td colspan="2">Co-Primary</td></tr>
<tr><td>To assess immunogenicity of COVISHIELD in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA assay</td><td>Ratio of Geometric mean titres (GMTs) of IgG antibodies against SARS-CoV-2 spike protein at 28 days after the second vaccination.</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>To assess the safety, tolerability and reactogenicity profile of the COVISHIELD</td><td>a) Occurrence of solicited local and/or systemic adverse events (AEs) for 7 days following each</td></tr>
</table>

	in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo	vaccination (Reactogenicity cohort) b) Occurrence of unsolicited adverse events for 28 days following each vaccination c) Occurrence of serious adverse events (SAEs) throughout the study duration following vaccination
	To assess immunogenicity of the COVISHIELD in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA and neutralizing antibody assays	a) Proportion with seroconversion for SARS-CoV-2 spike protein IgG at Day 29, Day 57 and Day 180 b) GMTs of IgG antibodies against SARS-CoV-2 spike protein at baseline, Day 29, Day 57 and Day 180 c) Proportion with seroconversion for virus neutralising antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Day 57 d) GMTs of Nab at baseline, and Day 57
	To compare the incidence of symptomatic COVID-19 disease between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo groups	Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 Note: Symptomatic COVID-19 cases which occur 14 days after each vaccination will be considered for analysis
	To compare the incidence SARS-CoV-2 infection between COVISHIELD,	Virologically confirmed (RT-PCR positive) cases of SARS-CoV-2. Note: Positive cases (symptomatic as

	Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo groups	well as asymptomatic) which occur 14 days after each vaccination will be considered for analysis.
	To compare the incidence of severe COVID-19 between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo groups	a) Hospitalizations due to COVID-19 b) Severe COVID-19 infection c) Intensive care unit (ICU) admissions associated with COVID-19 d) Deaths associated with COVID-19 Note: COVID-19 cases which occur 14 days after each vaccination will be considered for analysis
	Exploratory	
	To assess immunogenicity of the COVISHIELD in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 by neutralizing antibody assay and cell mediated immune response	a) Proportion with seroconversion for virus neutralising antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Day 29 and Day 180 b) GMTs of Nab at Day 29 and Day 180 c) Cell analysis by flow cytometry assays at baseline, Day 29, Day 57 and Day 180 including Spike specific T cell responses and cytokine levels
Study Design:	This is a Phase 2/3, observer-blind, randomised, controlled study in healthy adults in India, for comparison of the safety of COVISHIELD with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo, and immunogenicity with Oxford/AZ-ChAdOx1 nCoV-19 in prevention of SARS CoV-2 infection. A total of 1600 eligible participants of ≥ 18 years of age will be enrolled the study. Of these 400 participants will be part of immunogenicity cohort and will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19, respectively. The	

remaining 1200 participants from safety cohort will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Placebo, respectively.

Immunogenicity and Reactogenicity cohort: In the 400 participants (300 in COVISHIELD group and 100 in Oxford/AZ-ChAdOx1 nCoV-19 group) who agree to give blood for immunogenicity testing, approximately 10 ml blood sample will be collected at baseline, Day 29, Day 57 and Day 180. Additionally up to 20 ml blood sample will be collected from subset of 60 participants for assessment of cell mediated immune (CMI) responses at baseline, Day 29, Day 57 and Day 180. In the same cohort, data of solicited local and systemic adverse events through 7 days following each vaccination will be collected using participant diary cards. These 400 participants will be enrolled as below:

Age group	COVISHIELD	Oxford/AZ-ChAdOx1 nCoV-19	Total
18-59 years	225	75	300
≥ 60 years	75	25	100
Total	300	100	400

Eligible participants will receive two doses of 0.5 ml of either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 on Day 1 and Day 29 as per randomization. Post first vaccination site visits are planned on Days 29, 57 and 180. All participants will also be contacted telephonically on Day 90 for safety follow up.

Safety Cohort: 1200 participants in this cohort will receive two doses of 0.5 ml of either COVISHIELD (n=900) or Placebo (n=300) on Day 1 and Day 29 as per randomization. Post first vaccination site visits are planned on Days 29, 57 and 180. All participants will also be contacted telephonically on Day 90 for safety follow up.

Phase 2 part: Initial 100 participants will be enrolled and if there are no

	causally related SAEs as assessed by investigators during 7 days post first vaccination period then the study will progress to Phase 3 part of the study. **Phase 3 part:** Enrolment of remaining 1500 participants will be done if there are no causally related SAEs as assessed by investigators during 7 days post first vaccination period.
Inclusion and Exclusion Criteria	**Inclusion criteria:** Eligible participants must meet all of the below criteria at the time of enrolment: 1. Healthy adults aged ≥ 18 years of either sex. 2. Written informed consent by participants. 3. The participant is resident of the study area and is willing to comply with study protocol requirements, including availability for all scheduled visits of the study. 4. Healthy, as determined by medical history and physical examination. 5. Sexually active female participants of childbearing potential* must have practiced adequate contraception** for 28 days prior to study vaccine administration and agree to continue adequate contraception until completion of their Day 57 visit. * Females can be considered not of childbearing potential only if they have undergone bilateral tubal ligation or occlusion, or hysterectomy, or bilateral ovariectomy, or are post- menopausal (defined as continuous amenorrhea for12 months). ** Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label as follows: • Combined estrogen and progesterone oral contraceptives • Injectable progestogen • Implants of etenogestrel or levonorgestrel • Contraceptive vaginal ring

	• Percutaneous contraceptive patches • Intrauterine device or intrauterine system • Male partner (sole partner for participant) sterilized • Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive 6. Female participants of childbearing potential must have a negative urine pregnancy test within 24 hours prior to study vaccine administration. **Exclusion criteria:** Participants meeting any of the below criteria at the time of enrolment will be ineligible to participate in the trial. 1. Acute illness with or without fever at the time of study vaccine administration 2. History of laboratory confirmed COVID-19 infection / disease or known contact with a person that was infected with SARS-CoV-2 3. History of severe allergic reactions after previous vaccinations or hypersensitivity to any component of study vaccines 4. Any confirmed or suspected condition with impaired/altered function of immune system (e.g. immunodeficient or autoimmune conditions). 5. Have any bleeding disorder which is considered as a contraindication to intramuscular injection or blood draw. 6. Suspected or known current alcohol or drug dependence. 7. Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying drugs within three months prior to the study vaccination or planned use throughout the study period (For corticosteroids, this means prednisone, or equivalent, ≥ 0.5 mg/kg per day. Inhaled, intranasal and topical steroids are allowed). 8. Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months or

	planned use throughout the study period. 9. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban etc) 10. Administration of any vaccine within 28 days prior to enrolment in the study or planned administration of any vaccine during study participation. 11. Prior receipt of an investigational or licensed vaccine likely to impact interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines). 12. Current or planned participation in prophylactic drug trials for the duration of the study. 13. Use of any investigational or non-registered drug or vaccine within 30 days prior to the administration of study vaccines or planned during the study. 14. Pregnant or breast-feeding. 15. Individuals who are part of study team or close family members of individuals conducting this study. 16. Acute or chronic, clinically significant pulmonary, cardiovascular, metabolic, neurological, hepatic, or renal functional abnormality, as determined by medical history or physical examination. 17. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of the volunteer participating in the study or make it unlikely that the participant could complete the protocol.
Study Conduct:	The study will be initiated after permissions from the Drugs Controller General of India (DCGI) and Institutional Ethics Committee (IEC) of respective sites are obtained and registration of the study on Clinical Trial Registry of India (CTRI) is completed. The participants will be screened for eligibility after written informed consent is obtained. SARS-CoV-2 serology by ELISA/CLIA or any other equivalent method will be conducted. For this up to approximately 1.5 ml blood sample will

	be collected. In addition, a swab from nose and/or throat will be collected for RT-PCR test for SARS-CoV-2 infection. The eligible participants will be randomized on the day of screening itself as far as possible but not beyond 7 days from screening visit. In female participants of childbearing age, urine pregnancy test will be performed on the day of vaccination before randomizing the study participant and on Day 29 prior to second vaccination. If the participant presents with any acute illness with or without fever on Day 29 visit then second vaccination will be delayed till the event is resolved. A total of 1600 eligible participants will be randomized as mentioned above to receive study vaccine. The study vaccine will be injected intramuscularly in the deltoid as a 0.5 mL dose on Day 1 and Day 29. The participants will be observed closely for at least 30 minutes following vaccination. All the participants will be advised to take prophylactic paracetamol 1 gm every 6 hours for 24 hours after each vaccination. Participants will return to the clinical study site for follow up on Days 29 (+14 days), 57 (+14 days) and 180 (+28 days). They will also be contacted telephonically on Day 90 (±14). Approximately up to 10 ml blood sample will be collected at baseline, Day 29, Day 57 and Day 180 in immunogenicity cohort participants. Additional up to 20 ml blood sample will be collected from subset of 60 participants in immunogenicity cohort at baseline, Day 29, Day 57 and Day 180. Physical examination (PE) and vital sign evaluations will be performed and medical history and prior/concomitant medications will be captured during Screening (Full PE), Day 1, Day 29 (+14), Day 57 (+14) and Day 180 (+28) (Targeted PE for post vaccination visits). Vital sign measurement after 30 minutes (+30 minutes) post-vaccination will also be done.

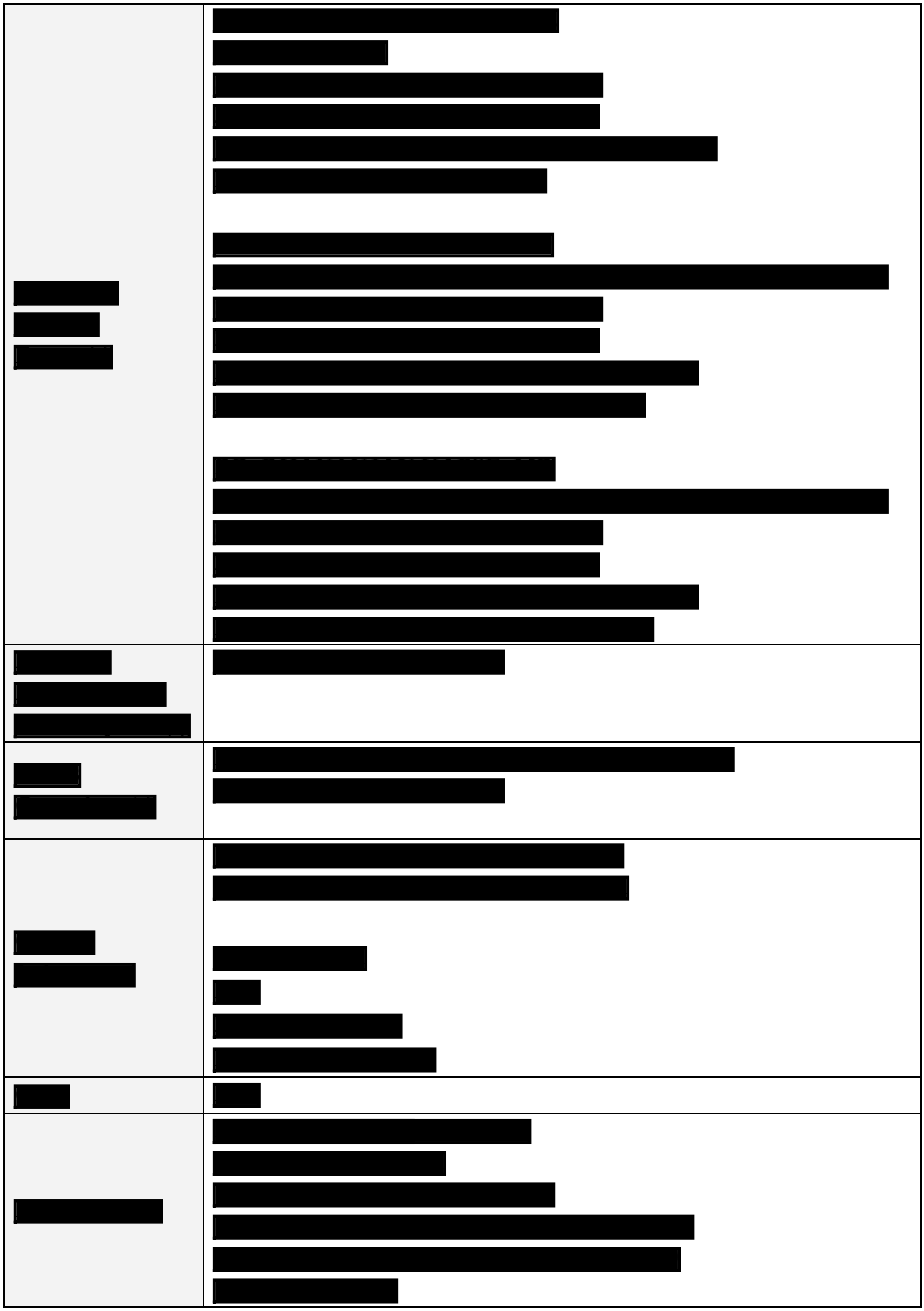
	Adverse Events (AE) 1. Unsolicited adverse events will be collected for 28 days post each vaccination in all the participants. 2. Serious adverse events (SAEs) will be collected throughout the study participation after vaccination in all the participants. 3. In reactogenicity cohort, solicited local and systemic adverse events will be actively collected for 7 days after each vaccination using diary cards. The solicited local AEs to be collected include pain, tenderness, redness, warmth, itch, swelling and induration. The solicited systemic AEs to be collected include fever, chills, headache, fatigue, malaise, arthralgia, myalgia and nausea. **Testing for COVID-19 during the study period:** Participants will be tested for COVID-19 if they present with a new onset of fever (≥38°C) OR cough OR shortness of breath OR anosmia/ageusia OR malaise OR fatigue OR history of contact with a confirmed COVID-19 positive case. Severe COVID-19 disease will be defined as clinical signs of severe pneumonia or acute respiratory distress syndrome or sepsis or septic shock using clinical criteria and clinical judgment. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate and other vital signs, need for ventilatory support, X-ray and CT scan imaging and blood test results, amongst other clinically relevant parameters. **Occurrence of COVID-19 disease in between first and second dose:** If the participant is confirmed with COVID-19 after the first dose but before the second dose, then the participant should be vaccinated with the second dose only two weeks after clinical recovery from COVID-19 disease. This is applicable, even if it is outside the recommended window period for the

	second dose. These participants will be continued in the study until Day 180 visit. In the light of Authorization for restricted use in emergency situation for COVISHIELD in India, the participants from the safety cohort may be unblinded if they have completed Day 90 telephonic contact (about two months post second dose) as per the study protocol and if they request the study team for unblinding. After unblinding of the eligible participants: • COVISHIELD group: No further action is required. These participants will be continued in the study as per protocol. • Placebo group: If the participant is willing to receive COVISHIELD then it will be administered as per the recommended dose and schedule. Even after unblinding, all study participants will be continued in the study for safety follow up till Day 180 as per study protocol.
Statistical considerations	The study is designed to have a 95% probability to detect at least one causally related serious adverse event among 1200 participants administered COVISHIELD, if the frequency of causally related serious adverse events is 1/400. It is planned to randomize 400 participants for the immunogenicity analysis for the study (300 to SII-ChAdOx1 nCoV-19 vaccine and 100 to Oxford-ChAdOx1 nCoV-19 vaccine). Assuming that the proportion of non-evaluable participants ≤ 21% (which leads to a sample size of 316 evaluable participants), the study will have at least 90 % power to show non-inferiority of immune responses assuming a Coefficient of Variation of 1.2 (which was estimated based on natural log-transformed IgG antibody titers against SARS-CoV-2 spike protein from the interim analysis of the phase 1/2 study of Oxford-ChAdOx1 nCoV-19 vaccine (Refer Investigator's Brochure). Non-inferiority will be concluded if the

	lower limit of the 95% CI for the GMT ratio for IgG antibodies against SARS-CoV-2 spike protein between SII-ChAdOx1 nCoV-19 vaccine and Oxford-ChAdOx1 nCoV-19 is > 0.67. Additional assumptions include a one-sided significance level of 0.025 and '0' difference in IgG antibody titers against SARS-CoV-2 spike protein between the two vaccine groups (i.e. a GMT ratio between both vaccine groups of 1). Sample size calculations were performed using a Non-inferiority test for the ratio of two means in PASS 15.0.7 Version software. Frequencies and estimate of the proportion of participants with safety events will be computed by vaccine group using two sided 95% Clopper-Pearson confidence intervals. The difference between the vaccines will be provided along with the two-sided 95% CIs obtained by the Miettinen and Nurminen method wherever applicable. ANCOVA will be fitted to the log transformed IgG antibodies against SARS-CoV-2 spike protein with terms for vaccine group, log baseline titer, age group and sex to compare the COVISHIELD against Oxford/AZ-ChAdOx1 nCoV-19 for co-primary endpoint. Individual mean and 95% CI values by treatment from this model will be used to generate the geometric mean titers with 95% CI at each time point and geometric mean ratio (GMR) with 95% CI at Visit 4 – Day 57 (+14) after second vaccination by back transforming to the original scale. The lower limit of the 95% CI for the GMR will be compared with a non-inferiority margin of 0.67 and COVISHIELD vaccine will be declared non-inferior to Oxford/AZ-ChAdOx1 nCoV-19 if > 0.67. Two interim analyses are planned as below: 1. Safety data of 28 days post second vaccination (Day 57) of all study participants 2. Immunogenicity data by IgG ELISA at 28 days post second vaccination (Day 57) of participants in immunogenicity cohort and safety data of 28 days post second vaccination (Day 57) of all study participants

1. GENERAL INFORMATION

Sponsor	**SERUM INSTITUTE OF INDIA PVT. LTD.** 212/2, Off Soli Poonawalla Road, Hadapsar, Pune-411028 [redacted]
Co-Sponsor	**Indian Council of Medical Research** V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, India
[redacted]	[redacted]



2. INTRODUCTION& BACKGROUND INFORMATION

2.1 INTRODUCTION

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV.[1] The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus.[2] Coronavirus disease 2019 (COVID-19) is the infectious disease caused by SARS-CoV-2.

By January 2020 there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARS- CoV-2 rapidly spread across the world. The WHO declared the COVID-19 outbreak a public health emergency of international concern on 30 January 2020. On March 11, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009.

As of June 08, 2020, there have been 6.9 million reported cases worldwide.[3] Importantly, as of June 08, 2020, India reported total confirmed cases of 266598 with 7466 fatalities as per data of Ministry of Health, Government of India.[4]

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors.[5] SARS-CoV-2 belongs to the phylogenetic lineage B of the genus Betacoronavirus and it recognizes the angiotensin-converting enzyme 2

(ACE2) as the entry receptor.[6] It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

The spike protein is a type I, trimeric, transmembrane glycoprotein located at the surface of the viral envelope of CoVs, which can be divided into two functional subunits: the N-terminal S1 and the C-terminal S2. S1 and S2 are responsible for cellular receptor binding via the receptor binding domain (RBD) and fusion of virus and cell membranes respectively, thereby mediating the entry of SARS-CoV-2 into target cells.[5] The roles of S in receptor binding and membrane fusion make it an ideal target for vaccine and antiviral development, as it is the main target for neutralising antibodies.

Although individuals of any age can acquire SARS-CoV-2, certain individuals are at a higher risk of infection with SARS-CoV-2. The high-risk group includes the health care workers (physicians and paramedical staff) working amid COVID-19 infected patients and all other people including household contacts of COVID-19 confirmed patients or people currently residing or working in COVID-19 hotspots/outbreak areas where there is a high risk of transmission of COVID-19 infection. The SARS-CoV-2 infections tend to be severe in population with co-morbidities or elderly population aged ≥ 60 years and therefore such subjects living or currently working in COVID-19 affected areas, are also considered high-risk population.

There is an urgent need to ensure the safety and health of existing health care workers and all other people living in SARS-CoV-2 infected areas where there is a high risk of disease transmission and find strategies to reduce the incidence, duration and intensity of SARS-CoV-2 infection among such population.

Currently, there is no specific antiviral treatment recommended for COVID-19, the current treatment strategy being only supportive. There are several vaccines in the various stages of clinical development and no vaccine has been marketed yet.

2.2 BACKGROUND

Live attenuated viruses have historically been among the most immunogenic platforms available, as they have the capacity to present multiple antigens across the viral life cycle in their native conformations. However, manufacturing live-attenuated viruses requires

complex containment and biosafety measures. Furthermore, live-attenuated viruses carry the risks of inadequate attenuation causing disseminated disease, particularly in immunocompromised hosts. Given that severe disease and fatal COVID-19 disproportionally affect older adults with co-morbidities, making a live- attenuated virus vaccine is a less viable option.

Replication competent viral vectors could pose a similar threat for disseminated disease in the immuno-suppressed. Replication deficient vectors, however, avoid that risk while maintaining the advantages of native antigen presentation, elicitation of T cell immunity and the ability to express multiple antigens.

Subunit vaccines usually require the use of adjuvants and whilst DNA and RNA vaccines can offer manufacturing advantages, they are often poorly immunogenic requiring multiple doses, which is highly undesirable in the context of a pandemic.

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

ChAdOx1 nCoV-19 vaccine has been already administered in more than 500 healthy adults of 18 to 55 years in Phase 1/2 study in United Kingdom (UK). A Phase 2/3 clinical efficacy study is ongoing in approximately 10,000 individuals of ≥ 5 years of age in UK. In addition, large Phase 3 clinical efficacy studies are ongoing in South Africa and Brazil. Also a large Phase 3 efficacy study is planned in USA. So far, no safety concerns are observed and the efficacy data from ongoing studies are awaited. COVISHIELD may also be used in these clinical efficacy studies.

We will get efficacy data on huge population for this vaccine from various countries. Considering the large safety and efficacy data from these studies, we have planned this Phase 2/3 safety and immunogenicity study in Indian population for licensure in India.

2.3 STUDY VACCINES

Oxford/AZ-ChAdOx1 nCoV-19:

Oxford University has developed a candidate vaccine ChAdOx1 nCoV-19. It consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigen of the SARS CoV-2 (nCoV-19), with a leading tissue plasminogen activator (tPA) signal sequence. ChAdOx1 nCoV-19 expresses a codon-optimized coding sequence for the Spike protein from genome sequence accession GenBank: MN908947. The tPA leader sequence has been shown to be beneficial in enhancing immunogenicity of another ChAdOx1 vectored CoV vaccine (ChAdOx1MERS).[7]

COVISHIELD (SII-ChAdOx1 nCoV-19):

After technology transfer between Oxford University, AstraZeneca and Serum Instiute of India Pvt Ltd., the same vaccine is manufactured at SIIPL. It is called as COVISHIELD (SII-ChAdOx1 nCoV-19).

Placebo:

Composition of Placebo is similar to COVISHIELD except that it will not contain active ingredient **(**adenovirus vector ChAdOx1, containing spike protein antigens of SARS-CoV-2).

2.3.1 Summary of Nonclinical Studies:

Refer to the Investigator Brochure for most recent non-clinical data update.

2.3.1.1 Immunogenicity (Jenner Institute, unpublished):

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

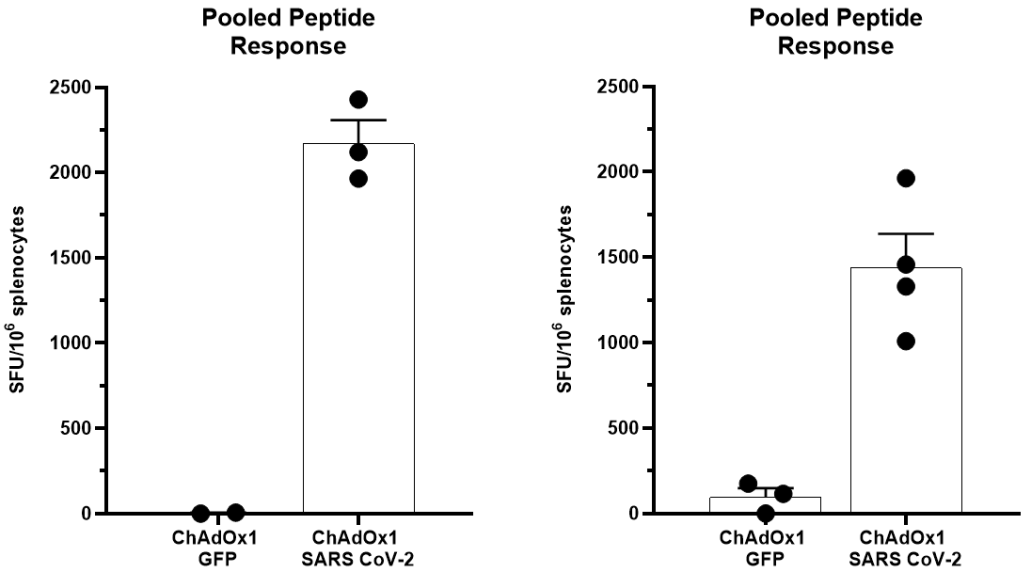


Figure 1. Summed splenic IFN-γ ELISpot responses of BALB/c (left panel) and CD-1 (right panel) mice, in response to peptides spanning the spike protein from SARS-CoV-2, nine or ten days post vaccination, with 1.7×10^{10} vp ChAdOx1 nCoV-19 or 8×10^{9} vp ChAdOx1 GFP. Mean with SEM are depicted

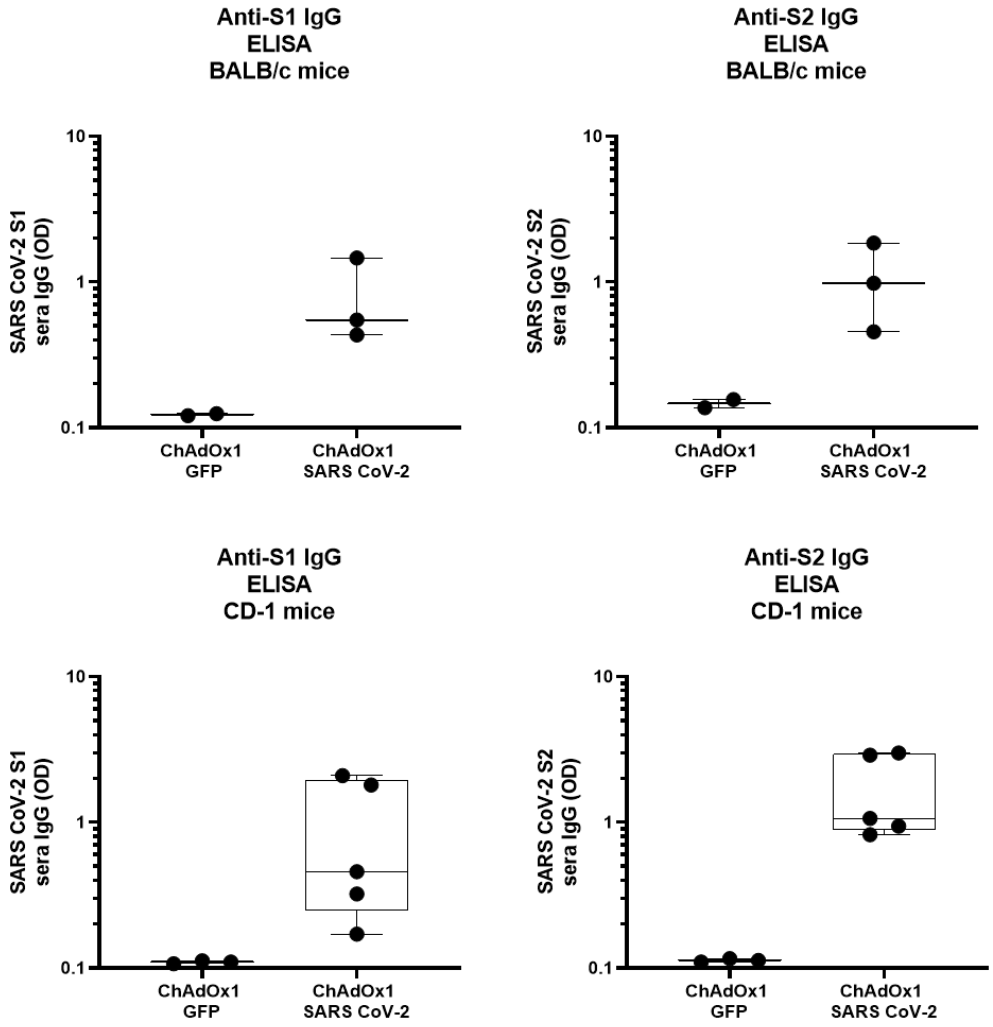


Figure 2. Box and whisker plot of the optical densities following ELISA analysis of BALB/C mouse sera (Top panel) incubated with purified protein spanning the S1 domain (left) or purified protein spanning the S2 domain (right) of the SARS-CoV-2 spike nine- or ten- days post vaccination, with 1.7×10^{10}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

A second experiment with a different dose was conducted.[8] Results are summarised in the figure below. Intracellular cytokine staining shows a pattern which is consistent with predominantly Th1 responses.

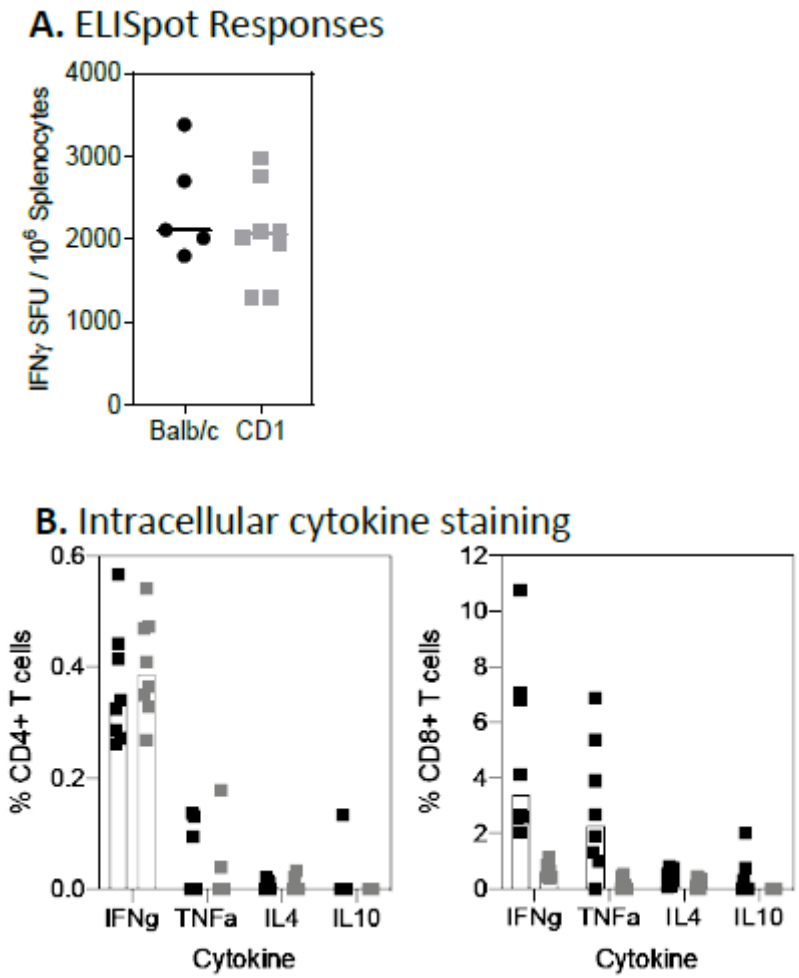


Figure 3. Antigen specific responses following ChAdOx1 nCov19 vaccination. BALB/c and outbred (CD1) mice were intramuscularly administered with 10^8 iu ChAdOx nCoV-19. 14 days later spleens harvested and cells stimulated peptides spanning the length of S1 and S2.

A. Graph show summed IFNg ELISpot responses in BALB/c (black circles) and outbred CD1 (grey squares) mice.

B. Graphs show the frequency of cytokine positive CD4 (left) or CD8 (right) T cells as measured by intracellular cytokine staining following stimulation of splenocytes with S1 pool (black) or S2 pool (grey) peptides in CD1 mice.

2.3.1.2 Efficacy*:*

Non-clinical efficacy studies of ChAdOx1 nCoV-19 in ferrets and non-human primates are in progress. Results will be included in the Investigator's Brochure when available.

2.3.1.3 Antibody Dependant Enhancement and Immunopathology:

Safety concerns around the use of full length coronavirus Spike glycoproteins and other

viral antigens (nucleoprotein) as a vaccine antigen have been raised following historical and limited reports of immunopathology and antibody dependent enhancement (ADE) reported *in vitro* and post SARS-CoV challenge in mice, ferrets and non-human primates (NHPs) immunised with whole SARS-CoV inactivated or full-length S protein based vaccines, including a study using Modified Vaccinia Ankara as a vector.[9-11] To date, there has been one report of lung immunopathology following MERS-CoV challenge in mice immunised with an inactivated MERS-CoV candidate vaccine.[12] However, in preclinical studies of ChAdOx1 immunisation and MERS-CoV challenge, no ADE was observed in hDPP4 transgenic mice, dromedary camels or non-human primates (van Doremalen et al, manuscript submitted). [13,14]

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

2.3.2 Clinical Studies

COV001 and COV002 are the first clinical studies employing ChAdOx1 nCoV-19. ChAdOx1 vectored vaccines expressing different inserts have previously been used in over 320 healthy volunteers taking part in clinical trials conducted by or in partnership with the University of Oxford in the UK and overseas (Table 1 and 2). Most importantly, a ChAdOx1 vectored vaccine expressing the full-length Spike protein from another Betacoronavirus, MERS-CoV, has been given to 31 participants to date as part of MERS001 and MERS002 trials. ChAdOx1 MERS was given at doses ranging from $5x10^9$ vp to $5x10^{10}$ vp (Table 2) with no serious adverse reactions reported. Further safety and immunogenicity results on ChAdOx1 MERS can be found on the Investigator's Brochure for ChAdOx1 nCoV-19 for reference.

Clinical trials of ChAdOx1 vectored vaccines encoding antigens for Influenza (fusion protein NP+M1), Tuberculosis (85A), Prostate Cancer (5T4), Malaria (LS2),

Chikungunya (structural polyprotein), Zika (prM and E), MERS-CoV (full-length Spike protein) and Meningitis B are listed in Tables 1 and 2.

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

Table 1: Clinical experience with ChAdOx1 viral vector vaccines

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	FLU004 (Influenza)	ChAdOx1 NP+M1	18-50	IM	5×10^8 vp	3	Antrobus et al, 2014. Molecular Therapy. DOI: 10.1038/mt.2013.284
					5×10^9 vp	3	
					2.5×10^{10} vp	3	
					5×10^{10} vp	6	
UK	FLU005 (Influenza)	ChAdOx1 NP+M1 MVA NP+M1 (week 8)	18-50	IM	2.5×10^{10} vp	12	Coughlan et al, 2018. EBioMedicine DOI: 10.1016/j.ebiom.2018.02.011 DOI: 10.1016/j.ebiom.2018.05.001
		ChAdOx1 NP+M1 MVA NP+M1 (week 52)	18-50	IM	2.5×10^{10} vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 8)	18-50	IM	2.5×10^{10} vp	12	
		MVA NP+M1 ChAdOx1 NP+M1 (week 52)	18-50	IM	2.5×10^{10} vp	9	
		ChAdOx1 NP+M1	>50	IM	2.5×10^{10} vp	12	
		ChAdOx1 NP+M1 MVA NP+M1 (week 8)	>50	IM	2.5×10^{10} vp	12	
UK	TB034 (Tubercuosis)	ChAdOx1 85A	18-50	IM	5×10^9 vp	6	Wilkie et al, 2020 Vaccine DOI:10.1016/j.vaccine.2019.10.102
					2.5×10^{10} vp	12	
		ChAdOx1 85A MVA85A (week 8)	18-50	IM	2.5×10^{10} vp	12	

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
		ChAdOx1 85A (x2, 4weeks apart) MVA85A (at 4 months)	18-50	IM	2.5×10^{10} vp	12	
Switzerland	TB039 (ongoing) (Tuberculosis)	ChAdOx1 85A	18-55	Aerosol	1×10^{9} vp	3	Clinicaltrials.gov:NCT04121494
				Aerosol	5×10^{9} vp	3	
				Aerosol	1×10^{10} vp	11	
				Aerosol/IM	1×10^{10} vp	15	
Uganda	TB042 (ongoing) (Tuberculosis)	ChAdOx1 85A	18-49	IM	5×10^{9} vp	6	Clinicaltrials.gov: NCT03681860
					2.5×10^{10}	6	
UK	VANCE01 (Prostate cancer)	ChAdOx1.5T4 MVA.5T4	18 – 75	IM	2.5×10^{10} vp	34	Clinicaltrials.gov: NCT02390063
UK	ADVANCE (ongoing) (Prostate cancer)	ChAdOx1.5T4 MVA.5T4	≥18	IM	2.5×10^{10} vp	23 (as of Feb 20)	Clinicaltrials.gov: NCT03815942
UK	VAC067 (Malaria)	ChAdOx1 LS2	18-45	IM	5×10^{9} vp	3	Clinicaltrials.gov: NCT03203421
					2.5×10^{10} vp	10	
UK	VAMBOX (Meningitis B)	ChAdOx1 MenB.1	18-50	IM	2.5×10^{10} vp	3	ISRCTN46336916
					5×10^{10} vp	26	
UK	CHIK001	ChAdOx1 Chik	18-50	IM	5×10^{9} vp	6	Clinicaltrials.gov: NCT03590392 DOI:
					2.5×10^{10} vp	9	

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
	(Chikungunya)				5×10^{10} vp	9	https://doi.org/10.4269/ajtmh.abstract 2019 Abstract #59, page 19.
UK	ZIKA001 (Zika)	ChAdOx1 Zika	18-50	IM	5×10^{9} vp	6	Clinicaltrials.gov: NCT04015648
					2.5×10^{10} vp	3 (as of Feb 20)	
					5×10^{10} vp	-	

Table 2: Clinical experience with ChAdOx1 MERS against MERS CoV

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	MERS001	ChAdOx1 MERS	18-50	IM	5×10^{9} vp	6	Clinicaltrials.gov: NCT03399578 DOI: https://doi.org/10.1016/S1473-3099(20)30160-2 .
					2.5×10^{10} vp	9	
					5×10^{10} vp	9	
					2.5×10^{10} vp (homologous prime- boost)	3	
Saudi Arabia	MERS002 (ongoing)	ChAdOx1 MERS	18-50	IM	5×10^{9} vp	4	Clinicaltrials.gov: NCT04170829
					2.5×10^{10} vp	3	
					5×10^{10} vp	-	

Table 3: Clinical Experience with ChAdOx1 nCoV-19

Country	Trial	Vaccine	Age	Route	Dose	Number of Volunteers (Received ChAdOx1)	Publication / Registration Number
UK	COV001	ChAdOx1 nCoV-19	18-55	IM	5×10^{10} vp	533	Clinicaltrials.gov: NCT04324606
					5×10^{10} vp (homologous prime-boost)	10	
UK	COV002	ChAdOx1 nCoV-19	18-55	IM	5×10^{10} vp	-	Clinicaltrials.gov: NCT04400838
			56-69			-	
			56-69		5×10^{10} vp (homologous prime-boost)	-	
			≥70		5×10^{10} vp	-	
			≥70		5×10^{10} vp (homologous prime-boost)	-	
			5-12		2.5×10^{10} vp	-	

The first clinical trial of the ChAdOx1 nCoV-19 candidate vaccine (COV001) started on April 23, after approval by the IRB and the Medicines and Healthcare Products Regulatory Agency (MHRA). The study included healthy adults between the ages of 18 and 55 at various research sites in the UK. The objectives of the study are to assess vaccine safety, reactogenicity and immunogenicity, as well as the collection and analysis of any confirmation of COVID-19 by PCR. These cases will be analyzed in a meta-analysis, together with case collections from other studies (methodology still under review). The study involved approximately 1070 individuals who are in the follow-up period. The Independent Safety Data Monitoring Committee, which continuously monitors the study, has so far not reported any concerns to the MHRA or the study sponsor (secure follow-up of one to four weeks per participant).

In addition, another phase II study (COV002) is initiated at various locations in the United Kingdom. In a first stage, this study will include 80 healthy adults from 56 to 69 years old, 120 elderly people over 70 with no upper age limit and 60 children from 5 to 12 years old. The assessed endpoints will be safety and immunogenicity, including T cell immunity. This study will be expanded in stage 2 to a phase III study of safety, immunogenicity and efficacy, including 10,000 adults over 18 years of age, with an increased risk of infection by COVID-19 at various research sites in the United Kingdom. The safety and efficacy assessments of the phase III part of the COV002 are the same as those of another phase III study (COV003) in Brazil. This will allow for the eventual grouping of effectiveness data between studies.

COV001 study interim safety and immunogenicity data:

Preliminary safety data on 44 volunteers receiving ChAdOx1 nCoV-19 as part of COV001 is shown below. There have been no serious adverse reactions associated with ChAdOx1 – nCoV-19 reported to date. The data below reflects 28 days of follow-up. In total 544 participants received at least 1 dose of ChAdOx1 nCoV-19 to date and 10 participants have received a booster dose.

COV001	
Synopsis Item	Description
Title	A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers.
Design	Phase I/II, multi-centre, single blinded, randomised controlled trial
Location	Oxford, UK
Start date	First visit of first volunteer 23/04/2020
Study status	Ongoing
Number of subjects	1,077 (of those 544 received ChAdOx1 nCoV-19)
Sex	Male, female
Age	Adults aged 18-55
Health status	Healthy
Dose group(s)	Groups 1, 2 and 4: 5×10^{10} vp (single dose) Group 3: 5×10^{10} vp (two doses, 4 weeks apart)
Control injection	MenACWY
Administration route	All IM
Safety	• No serious adverse reactions (SARs) or suspected unexpected serious adverse reactions (SUSARs) related to ChAdOx1 nCoV-19 occurred to date. • The majority of adverse events (AEs) reported were self-limiting and mild or moderate in severity, but severe events have also been reported with their onset within the first 72h (most frequently within the first 24h). • Vaccine site pain and tenderness were the most common local adverse event and was predominantly mild in severity, with occasional moderate and severe events described. • Chills, feverishness, fevers, headache, malaise and myalgia were relatively common systemic AEs being predominantly mild or moderate in nature. • The vaccine was tolerated despite the reactogenicity profile, with no safety concerns. • The vast majority of solicited local and systemic AEs were short-lived and resolved within 1-7 days.
Immunogenicity **(Table 4)**	Preliminary immunogenicity data suggest a single dose of ChAdOx1 nCoV-19 is able to elicit both humoral and cellular responses. A summary of preliminary findings is described below.
Publication	In preparation

Table 4: Data Summaries for ELISA and ELISpot data – Group 1

Assay	Visit Day	Vaccine	N	Median [IQR]	GMT (95% CI)	*Wilcoxon Rank-Sum p value*	GMR (compared to D0) (95% CI)	*% > 4-fold rise from baseline*
SARS-CoV-2 spike protein-specific IgG end-point ELISA	0	ChAdOx1-nCOV-19	44	50.0 [50.0, 50.0]	56.0 (47.6, 65.8)			
	0	MenACWY	44	50.0 [50.0, 50.0]	53.2 (47.0, 60.2)			
	14	ChAdOx1-nCOV-19	44	297.1 [152.1, 474.6]	299.7 (205.7, 436.7)		5.4 (3.8, 7.5)	64%
						<0.0001		
	14	MenACWY	44	50.0 [50.0, 50.0]	53.0 (47.2, 59.5)		1.0 (1.0, 1.0)	0%
	28	ChAdOx1-nCOV-19	42	675.7 [407.8, 1604.3]	802.4 (601.8, 1069.8)		14.3 (10.7, 19.1)	95%
						<0.0001		
	28	MenACWY	43	50.0 [50.0, 50.0]	52.6 (47.5, 58.3)		1.0 (1.0, 1.0)	0%
IFNg ELISpot response to SARS- CoV-2 spike protein	0	ChAdOx1-nCOV-19	43	85.3 [48.0, 154.7]	95.2 (76.6, 118.3)			
	0	MenACWY	43	81.3 [48.0, 145.3]	92.8 (76.0, 113.3)			
	7	ChAdOx1-nCOV-19	40	183.2 [76.3, 350.0]	179.0 (132.0, 242.6)		2.0 (1.5, 2.6)	15%
						0.0003		
	7	MenACWY	43	67.3 [48.0, 120.0]	82.2 (68.6, 98.6)		0.9 (0.7, 1.1)	0%
	14	ChAdOx1-nCOV-19	43	856.0 [469.3, 1848.0]	878.7 (656.3, 1176.4)		9.1 (6.3, 13.2)	74%
						<0.0001		
	14	MenACWY	44	55.3 [48.0, 100.0]	73.5 (61.8, 87.5)		0.8 (0.6, 1.0)	0%
	28	ChAdOx1-nCOV-19	42	512.0 [260.0, 1034.7]	497.4 (358.1, 690.8)		5.0 (3.3, 7.4)	46%
						<0.0001		
	28	MenACWY	41	48.7 [48.0, 79.3]	64.1 (55.8, 73.7)		0.7 (0.6, 0.8)	0%

2.4 RATIONALE FOR STUDY DESIGN

This is a Phase 2/3, observer-blind, randomised, controlled study in healthy adults in India, for comparison of the safety of COVISHIELD with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo, and immunogenicity with Oxford/AZ-ChAdOx1 nCoV-19 in prevention of SARS CoV-2 infection.

The proposed study will enroll healthy adults aged ≥ 18 years. Deaths from SARS-CoV-2 infections are more common in adults aged 65 or older, and in those with pre- existing co-morbidities such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer. SARS-CoV-2 infects children as well as adults and the elderly. However, SARS-CoV-2 infections in children are less severe and rarely result in death. It is the oldest age group that is most at risk of death following natural infection, and in whom the vaccine would most likely be used first if deployed in a future public health campaign.

Immunogenicity and Reactogenicity cohort:

Oxford/AZ-ChAdOx1 nCoV-19 vaccine has been selected as an active control in order to bridge COVISHIELD vaccine with Oxford/AZ-ChAdOx1 nCoV-19 vaccine. Currently three clinical efficacy trials are ongoing with Oxford/AZ-ChAdOx1 nCoV-19 vaccine in UK, Brazil and South Africa.

Safety cohort:

Currently there is no licensed vaccine available against COVID-19. The active control that is planned to be used in the immunogenicity cohort is in short supply and it is not available to use in 300 participants in safety cohort. There is no licensed two dose schedule vaccine to be used in adults. Therefore placebo will be used as a comparator in safety cohort for comparison of safety with COVISHIELD.

3. OBJECTIVES AND ENDPOINTS

3.1 PRIMARY AND CO-PRIMARY OBJECTIVE(S) AND ESTIMAND(S)

Primary and co-primary Objective(s)	**Estimand Description (including *Endpoint*)**
To assess the safety of COVISHIELD.	**Estimand 1 (Primary)** Proportion of participants with at least one causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination. A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination Infections and death (meeting criteria) are included in the endpoint (composite strategy). **Endpoint** Occurrence of causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination.
To assess immunogenicity of COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA assay.	**Estimand 2 (Co-Primary)** Ratio of geometric mean titres (GMTs) of IgG antibodies against SARS-CoV-2 spike protein in healthy individuals at Visit 4 – Day 57 (+14) after second vaccination between vaccines (COVISHIELD/ Oxford/AZ-ChAdOx1 nCoV-19). Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines or missed 2nd vaccine or death. **Endpoint** • IgG antibodies against SARS-CoV-2 spike protein at Visit 4 – Day 57 (+14) after second vaccination.

3.2 SECONDARY OBJECTIVES AND ESTIMANDS

Secondary Objective(s)	Estimand Description (including *Endpoint*)
To assess the safety, tolerability and reactogenicity profile of the COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo.	**Estimand 3** Proportion participants at least one SAEs, and proportion with at least one Unsolicited AEs • Up to Visit 6 – Day 180 (+28) following first vaccination with SAE • Within 28 days following each vaccination with Unsolicited AEs. A treatment policy strategy is used for assessing safety irrespective of use of immune modifying medications or other vaccinations and missed 2nd dose of vaccine. Infections and death are included in the endpoint (composite strategy). **Endpoints** • Occurrence of SAEs Up to Visit 6 – Day 180 (+28) following first vaccination. • Occurrence Unsolicited AEs for 28 days following each vaccination. **Estimand 4** Proportion participants at least one solicited local and/or systemic adverse events (AEs) • Within 7 days following each vaccination. A treatment policy strategy is used for assessing safety irrespective of use of modifying medications and to assess missed 2nd vaccine dose. composite strategy is used to understand safety without subsequent infection. While on treatment strategy is used to utilize all available data until event. **Endpoint** • Occurrence of solicited local and systemic adverse events (AEs) for 7 days following vaccination (Reactogenicity cohort)
To assess immunogenicity of the COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA and neutralizing antibody assays.	**Estimand 5** GMTs of Nab at Baseline and Visit 4 – Day 57 (+14) and GMTs of IgG antibodies against SARS-CoV-2 spike protein at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death. **Endpoints** • NAb against SARS-CoV-2 spike protein at baseline and Day 57. • IgG antibodies against SARS-CoV-2 spike protein at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28)

Secondary Objective(s)	Estimand Description (including *Endpoint*)
	Estimand 6 Proportion of participants with seroconversion for virus neutralizing antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and proportion participants with seroconversion for SARS-CoV-2 spike protein IgG at Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death. **Endpoints** • Seroconversion for NAb using live and/or pseudotype SARS-CoV-2 virus at Day 57. • Seroconversion for SARS-CoV-2 spike protein IgG at Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). Please note seroconversion is defined as four-fold increase in the titer from baseline.
To compare the incidence of symptomatic COVID-19 disease between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. To compare the incidence SARS-CoV-2 infection between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. To compare the incidence of severe COVID-19 between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine.	**Estimand 7** Proportion of participants with incidence of confirmed (RT-PCR positive) symptomatic cases of COVID-19, virologically confirmed (RT-PCR positive) cases of COVID-19, Severe COVID-19 infection, Intensive care unit (ICU) admissions associated with COVID-19, Hospitalizations due to COVID-19 and Deaths associated with COVID-19 from post 14 days post-vaccination until the end of the study visit 6 – Day 180 (+28). A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination. Infections and death (meeting criteria) are included in the endpoint (composite strategy). **Endpoint** • Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Virologically confirmed (RT-PCR positive) cases of SARS-CoV-which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Severe COVID-19 infection which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Intensive care unit (ICU) admissions associated with COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28) • Hospitalizations due to COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Deaths associated with COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28).

3.3 EXPLORATORY OBJECTIVES AND ESTIMANDS

Exploratory Objective(s)	Estimand Description (including *Endpoint*)
To assess immunogenicity of the COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by neutralizing antibody assay and cell mediated immune response.	**Estimand 8** GMTs of NAb at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) [Same hypothetical strategies as for Estimand 5] **Endpoints** • NAb against SARS-CoV-2 spike protein at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). **Estimand 9** Proportion of participants with seroconversion for virus neutralizing antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). [Same hypothetical strategies as for Estimand 6] **Endpoints** • Seroconversion for NAb using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). **Estimand 10** Mean spike specific T cell responses and cytokine levels along with confidence interval at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) **Endpoints** • Spike specific T cell responses and cytokine levels at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28)

4. STUDY DESIGN

This is a Phase 2/3, observer-blind, randomised, controlled study in healthy adults in India, for comparison of the safety of COVISHIELD with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo, and immunogenicity with Oxford/AZ-ChAdOx1 nCoV-19 in prevention of SARS CoV-2 infection.

A total of 1600 eligible participants of ≥ 18 years of age will be enrolled the study. Of these 400 participants will be part of immunogenicity cohort and will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19, respectively. The remaining 1200 participants from safety cohort will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Placebo, respectively.

Immunogenicity and Reactogenicity cohort: In the 400 participants (300 in COVISHIELD group and 100 in Oxford/AZ-ChAdOx1 nCoV-19 group) who agree to give blood for immunogenicity testing, approximately 10 ml blood sample will be collected at baseline, Day 29, Day 57 and Day 180. Additionally up to 20 ml blood sample will be collected from subset of 60 participants for assessment of cell mediated immune (CMI) responses at baseline, Day 29, Day 57 and Day 180. In the same cohort, data of solicited local and systemic adverse events through 7 days following each vaccination will be collected using participant diary cards. These 400 participants will be enrolled as below:

Age group	COVISHIELD	Oxford/AZ-ChAdOx1 nCoV-19	Total
18-59 years	225	75	300
≥ 60 years	75	25	100
Total	300	100	400

Eligible participants will receive two doses of 0.5 ml of either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 Placebo on Day 1 and Day 29 as per randomization. Post first vaccination site visits are planned on Days 29, 57 and 180. All participants will also be contacted telephonically on Day 90 for safety follow up.

Safety Cohort: 1200 participants in this cohort will receive two doses of 0.5 ml of either COVISHIELD (n=900) or Placebo (n=300) on Day 1 and Day 29 as per randomization. Post first vaccination site visits are planned on Days 29, 57 and 180. All participants will also be contacted telephonically on Day 90 for safety follow up.

Phase 2 part: Initial 100 participants will be enrolled and if there are no causally related SAEs as assessed by investigators during 7 days post first vaccination period then the study will progress to Phase 3 part of the study.

Phase 3 part: Enrolment of remaining 1500 participants will be done if there are no causally related SAEs as assessed by investigators during 7 days post first vaccination period.

Table 5: Schedule of study events

Visit Number	1 (Screening Visit)*	2*	3	4	5 (Telephonic contact)	6
Visit time and window	**Upto -7 Days from Day 1**	**Day 1**	**Day 29 (+14)**	**Day 57 (+14)**	**Day 90 (±14)**	**Day 180 (+28)**
Informed Consent	X					
Demographic Data	X					
Medical History	X	X[a]				
General Physical Examination & vital signs	X	X[a]	X[e]	X[e]		X[e]
Urine pregnancy test[d]		X[a]	X[a]			
Exclusion/Inclusion Criteria	X	X[a]				
Randomization		X[a]				
Blood Collection[b]	X[a]		X[a]	X		X
Study Vaccination		X	X			
30-Minute Post-Vaccination Assessment		X	X			
Nose and/or throat swab[g]	X		X			X
Issue of diary card[f]		X	X			
Review and collection of diary card[f]			X	X		
Recording of solicited AEs[f]		*7 days post vaccination*	*7 days post vaccination*			
Recording of unsolicited AEs		*28 days post vaccination*				
Reporting of SAEs		*Throughout the study period*				
Recording of concomitant medications and vaccinations including prophylactic paracetamol[h]		*Throughout the study period [c]*				

* Visit 2 procedures should happen on the day of screening visit itself as far as possible but not beyond 7 days from screening visit.

a. Procedure to be performed prior to vaccination
b. At screening visit approx. 1.5 mL of blood to be drawn from all participants to determine serological evidence of infection.
   For immunogenicity cohort: Approx. 10 ml blood to be drawn prior to vaccination either on screening visit or Visit 2 (Day 1) as baseline sample and also at Day 29, Day 57 and Day 180.
   For subset of 60 participants in immunogenicity cohort: Additionally up to 20 ml blood to be drawn prior to vaccination either on screening visit or Visit 2 (Day 1) as baseline sample and also at Day 29, Day 57 and Day 180.
c. Beyond Day 57, only the concomitant medications indicated for SAEs, if any will be recorded
d. Only among females participants of child bearing potential.
e. A targeted physical examination (only at post vaccination visits) will be performed if there has been any AE reported since the previous visit that has not already been recorded and closed within unscheduled visits
f. Applicable only for participants in immunogenicity and reactogenicity cohort
g. If the participant presents with a new onset of fever (>38°C) OR cough OR shortness of breath OR anosmia/ageusia OR malaise OR fatigue then a swab from nose and/or throat will be collected for RT-PCR testing for SARS-CoV-2 infection at any time post-vaccination apart from scheduled timepoints.
h. All the participants will be advised to take prophylactic paracetamol 1 gm every 6 hours for 24 hours after each vaccination.

5. STUDY POPULATION

5.1 INCLUSION CRITERIA

Eligible participants must meet all of the below criteria at the time of enrolment:

1. Healthy adults aged ≥ 18 years of either sex.
2. Written informed consent by participants.
3. The participant is resident of the study area and is willing to comply with study protocol requirements, including availability for all scheduled visits of the study.
4. Healthy, as determined by medical history and physical examination.
5. Sexually active female participants of childbearing potential* must have practiced adequate contraception** for 28 days prior to study vaccine administration and agree to continue adequate contraception until completion of their Day 57 visit.

   * Females can be considered not of childbearing potential only if they have undergone bilateral tubal ligation or occlusion, or hysterectomy, or bilateral ovariectomy, or are post- menopausal (defined as continuous amenorrhea for12 months).

   ** Adequate contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label as follows:

   - Combined estrogen and progesterone oral contraceptives
   - Injectable progestogen
   - Implants of etenogestrel or levonorgestrel
   - Contraceptive vaginal ring
   - Percutaneous contraceptive patches
   - Intrauterine device or intrauterine system
   - Male partner (sole partner for participant) sterilized
   - Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository), and/or progesterone alone oral contraceptive
6. Female participants of childbearing potential must have a negative urine pregnancy test within 24 hours prior to study vaccine administration.

5.2 EXCLUSION CRITERIA

Participants meeting any of the below criteria at the time of enrolment will be ineligible to participate in the trial.

1. Acute illness with or without fever at the time of study vaccine administration
2. History of laboratory confirmed COVID-19 infection / disease or known contact with a person that was infected with SARS-CoV-2
3. History of severe allergic reactions after previous vaccinations or hypersensitivity to any component of study vaccines
4. Any confirmed or suspected condition with impaired/altered function of immune system (e.g. immunodeficient or autoimmune conditions)
5. Have any bleeding disorder which is considered as a contraindication to intramuscular injection or blood draw
6. Suspected or known current alcohol or drug dependence
7. Chronic administration (defined as more than 14 days) of immunosuppressant or other immune-modifying drugs within three months prior to the study vaccination or planned use throughout the study period. (For corticosteroids, this means prednisone, or equivalent, ≥ 0.5 mg/kg per day. Inhaled, intranasal and topical steroids are allowed)
8. Administration of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months or planned use throughout the study period
9. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban etc)
10. Administration of any vaccine within 28 days prior to enrolment in the study or planned administration of any vaccine during study participation.
11. Prior receipt of an investigational or licensed vaccine likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines).
12. Current or planned participation in prophylactic drug trials for the duration of the study.
13. Use of any investigational or non-registered drug or vaccine within 30 days prior to the administration of study vaccines or planned during the study.
14. Pregnant or breast-feeding.
15. Individuals who are part of study team or close family members of individuals conducting this study.

16. Acute or chronic, clinically significant pulmonary, cardiovascular, metabolic, neurological, hepatic, or renal functional abnormality, as determined by medical history or physical examination.
17. Any other condition that in the opinion of the investigator would jeopardize the safety or rights of the volunteer participating in the study or make it unlikely that the participant could complete the protocol.

6. TREATMENT OF STUDY PARTICIPANTS

6.1 DESCRIPTION OF STUDY VACCINES

The term 'study vaccine' refers to those vaccines provided by the Sponsor, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described below.

COVISHIELD (SII-ChAdOx1 nCoV-19):

COVISHIELD consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2.

Composition:

Each dose of 0.5 mL of COVISHIELD contains 5 X 10^{10} VP.

Ingredient	Final Concentration	per dose (0.5mL)	Unit
L-Histidine	10mM	0.776	mg
Sucrose	0.075	37.5	mg
Sodium chloride	35mM	1.0225	mg
Magnesium Chloride (MgCl2.6H20)	1mM	0.1015	mg
Polysorbate 80	0.001	0.0005	mL
EDTA (Edetate Disodium)	0.1mM	0.017	mg
Ethanol	0.005	0.0025	mL
HCl	q.s. for pH Adjustment		
pH	6.1 to 7.1		

Formulation: Ready to use liquid formulation in a 5 mL vial.

Route of administration: Intramuscular

Site of injection: Deltoid muscle

Dose: 0.5 ml containing 5 x 10^{10} VP

Dose schedule: Two doses 4 weeks apart (First dose on Day 1and Second dose on Day 29)

Oxford/AZ-ChAdOx1 nCoV-19 vaccine:

Oxford/AZ-ChAdOx1 nCoV-19 vaccine consists of the replication-deficient simian adenovirus vector ChAdOx1, containing the structural surface glycoprotein (Spike protein) antigens of SARS-CoV-2.

Composition: Each dose of 0.5 mL of Oxford/AZ-ChAdOx1 nCoV-19 vaccine contains 5 x 10^{10} VP.

Ingredient	Final Concentration
L-Histidine	10mM
Sucrose	0.075
Sodium chloride	35mM
Magnesium Chloride (MgCl2.6H20)	1mM
Polysorbate 80	0.001
EDTA (Edetate Disodium)	0.1mM
Ethanol	0.005
HCl	q.s. for pH Adjustment
pH	~6.6

Formulation: Ready to use liquid formulation in a vial.

Route of administration: Intramuscular

Site of injection: Deltoid muscle

Dose: 0.5 ml containing 5 x 10^{10} VP

Dose schedule: Two doses 4 weeks apart (First dose on Day 1and Second dose on Day 29)

Placebo:

Composition of Placebo is similar to COVISHIELD except that it will not contain active ingredient **(**adenovirus vector ChAdOx1, containing spike protein antigens of SARS-CoV-2).

Composition:

Ingredient	Final Concentration	per dose (0.5mL)	Unit
L-Histidine	10mM	0.776	mg
Sucrose	0.075	37.5	mg
Sodium chloride	35mM	1.0225	mg
Magnesium Chloride (MgCl2.6H20)	1mM	0.1015	mg
Polysorbate 80	0.001	0.0005	mL
EDTA (Edetate Disodium)	0.1mM	0.017	mg
Ethanol	0.005	0.0025	mL
HCl	q.s. for pH Adjustment		
pH	6.1 to 7.1		

Formulation: Ready to use liquid formulation in a vial.

Route of administration: Intramuscular

Site of injection: Deltoid muscle

Dose: 0.5 ml

Dose schedule: Two doses 4 weeks apart (First dose on Day 1and Second dose on Day 29)

6.2 PRECAUTIONS TO BE OBSERVED IN ADMINISTRATING STUDY VACCINES

Prior to vaccination, participants must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be

disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. DO NOT inject intravascularly.

As with all vaccines, appropriate medical treatment (like adrenaline 1:1000, anti-histamine (diphenhydramine), corticosteroids (hydrocortisone) and resuscitation equipment etc.) must be available at the site, and staff and supervision must be readily available in case of rare anaphylactic or any severe allergic reactions following administration of the study vaccine.

Prompt use of resuscitation measure can be lifesaving and must be implemented at the first suspicion of anaphylaxis.

6.3 PREPARATION AND ADMINISTRATION OF THE STUDY VACCINE

Study vaccines are available as a ready to use vial and does not need any reconstitution. A vial will be removed from cold storage and inspected to confirm the absence of particulate materials. ChAdOx1 nCoV-19 will be allowed to thaw to room temperature and will be administered in accordance with Pharmacy manual. Using needle and syringe 0.5 ml volume from vial will be withdrawn and injected intramuscularly.

Study vaccine should be visually inspected before administration and in the event of any foreign particulate matter and/or any unusual appearance of the study vaccine, vial will be set aside and monitor informed.

The study vaccine will be administered as per randomization schedule via intramuscular injection on Day 1 and Day 29. Preferred site of injection is deltoid muscle. The study vaccines are supplied as multidose vials however only a single dose of 0.5 ml will be used from each vial for a single participant for each vaccination. The vial with the remaining volume will kept securely at site for accountability by study monitor.

The investigator or designee will be responsible for oversight of the administration of vaccine to participants enrolled in the study according to the procedures presented in this study protocol. All vaccines will be prepared and administered only by designated personnel who are qualified to perform that function.

Study vaccine to be administered to the participants must be stored in a safe and locked place with no access by unauthorized personnel.

6.4 VACCINE SUPPLY, LABELLING, STORAGE, ACCOUNTABILITY AND DISPOSAL

The sponsor will ensure the following:

- Appropriate supply of the study vaccines;
- Appropriate labeling of all study vaccines that complies with regulatory requirements.

The investigator must ensure the following:

- Availability of appropriately trained site staff to manage vaccine supply, accountability, preparation and administration.
- Acknowledge receipt of the study vaccines by site staff, including confirmation that the vaccines:
    - were received in good condition;
    - remained within the appropriate temperature range during shipment from the sponsor to the investigator's designated storage location;
    - have been confirmed by the sponsor as authorized for use
- Proper storage of the study vaccines, including:
    - storage in a secure, locked, temperature-controlled location;
    - proper storage according to the instructions specified on the labels;
    - appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature
- Appropriate use of the study vaccines, including:
    - use only in accordance with the approved protocol;
    - proper handling, including confirmation that the vaccine has not expired prior to administration;
    - appropriate documentation of administration of vaccines to study participants including:
        - Date, dosage, batch number, screening number assigned to participants, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor;
        - Proper reconciliation of all study vaccines received from the sponsor. Reconciliation is defined as maintaining records of which and how many

vaccines were received, which vaccines (and volume thereof) were administered to participants, and which vaccines were destroyed at the site.

- Vaccine will be either destroyed at site after sponsor approval or can be returned back to sponsor. Site will provide adequate documentation of destruction in the former case.

The study vaccines will be stored at +2°C to +8°C in a secure refrigerator. The storage temperature of the vaccines will be monitored daily with temperature monitoring devices and will be recorded.

Vaccines that have been stored differently from the manufacturer's instructions must not be used unless the sponsor provides written authorization for use. Any temperature deviation, i.e. temperature outside the range, must be reported to the sponsor as soon as detected. Following the exposure to such a temperature deviation, vaccines will not be used until written approval has been given by the sponsor. Expired vaccines must not be administered.

In the event that the use cannot be authorized, the sponsor will make every effort to replace the vaccine supply.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the trial.

7. STUDY PROCEDURES

7.1 GENERAL CONSIDERATIONS

The study will be initiated only after approvals from each site's Institutional ethics committee (IEC) and the DCGI have been obtained.

The schedules of evaluations and procedures that must be performed at specific time points are described in the following sections and in table 5.

7.2 STUDY VISITS

Visit #1 – Screening (Up to -7 Days from Day 1)

Potential participants will be informed about the scope of the study and the possibility of their inclusion in the study. If they are willing to participate, informed consent will be obtained. A signed (or thumb print with witness signature) and dated informed consent must be obtained by

the principal investigator (PI) or the designee before initiating any study specific procedures. The informed consent document used for the purpose must be approved by local IEC.

The process of obtaining informed consent should be documented in the source documents in addition to maintaining the original signed and dated informed consent at the site. A copy of the consent form will be given to the participants.

The participants will be screened for eligibility by the site staff under the direction of the PI after the informed consent process has been completed. All participants screened for the study will be assigned a screening ID.

All participants who have consented will be included into the screening cohort and will be evaluated for eligibility.

The following procedures will be completed for each participant prior to inclusion in the study.

- Demography (Age, sex, height and weight)
- Medical History (significant past and concurrent conditions, family history, history of allergies and vaccinations)
- Complete physical Examination (general, head, eyes, ears, nose, oropharynx, neck, lymph nodes (neck, supraclavicular, axillary, inguinal), abdomen, skin (especially injection sites), respiratory, cardiovascular system, musculoskeletal central nervous system and genitourinary system and perineum) including vital signs measurements (temperature, resting blood pressure, pulse and respiratory rate)
- Relevant prior and Concomitant medications
- Approximately 1.5 ml blood sample will be collected for SARS-CoV-2 serology by Enzyme-linked Immunosorbent Assay (ELISA) / Chemiluminescence Immunoassay (CLIA) or any other equivalent method
- A swab from nose and/or throat will be collected for Reverse Transcription Polymerase Chain Reaction (RT-PCR) testing for SARS-CoV-2 infection

The participants who are ineligible for the study or not randomized will be documented as screen failures on the Screening Log. The reason for screen failure must be documented.

A complete review of inclusion/exclusion criteria will be conducted. Participants who satisfy all inclusion criteria and none of the exclusion criteria will be enrolled.

Visit#2 (Day 1): Enrolment, Randomization and First Vaccination:

Visit 2 procedures should happen on the day of screening visit itself as far as possible but not beyond 7 days from screening visit.

During this visit (if separate from screening visit) participants will be asked about any intervening medical history since the visit 1 and targeted physical examination will be carried out if required.

In case of female participants of child bearing potential urine pregnancy test (UPT) will be performed prior to randomization.

Randomization:

The eligible participants will be randomized on the day of screening itself as far as possible but not beyond 7 days from screening visit. The eligible participants will be randomized via an Interactive Web Response System (IWRS).

If for any reason, after signing the informed consent form, the participant (who has passed screening) fails to be randomized, the reason for not being randomized should be recorded in source documents.

Blinding:

The study is designed as an observer-blind study. The study participants and the study personnel responsible for the evaluation of any study endpoints (e.g. safety and reactogenicity) will be unaware which study vaccine is administered. At each site only designated unblinded study personnel will be involved in getting randomization code by accessing IWRS, vaccine preparation and administration. These unblinded personnel will not participate in any of the study endpoint evaluations. All other site personnel will remain blinded to the study vaccine administration.

The sponsor personnel involved in the study will also remain blinded. The CRO will designate an unblinded monitor(s) and a statistician who may be able to access the subject level unblinded data as per the need. Other CRO personnel working on the trial will remain blinded.

The laboratories involved in the immunological testing will be blinded to the treatment assignment.

Prior to Vaccination:

Immunogenicity cohort: Approximately 10 ml blood will be collected from participants in immunogenicity cohort for immunological testing prior to vaccination either on screening visit or Visit 2 i.e. Day 1. Additionally up to 20 ml blood sample will be collected from subset of 60 participants for assessment of CMI responses. This will be a baseline sample.

Study Vaccination (First dose):

The participant will receive first dose of 0.5 ml of either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 vaccine or Placebo as per the randomization schedule.

Post - Vaccination Activities:

The participants will be observed closely for at least 30 minutes following vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine. After 30 minutes (+30 minutes) post vaccination any solicited local and systemic AEs, any unsolicited AEs and Vitals (temperature, resting blood pressure, pulse and respiratory rate) will be recorded.

The participants in reactogenicity cohort will receive a thermometer, scale and a diary. These participants/parents will be trained by the site personnel for recording and documenting any solicited reactions and AEs they may experience and concomitant medications they may use within 7 days following vaccination in the diary. The participants will be informed to visit the site on Day 29 and carry this completed diary at the time of visit.

The investigator or a delegate should ensure that all information are recorded in the source documents and accurately transcribed in the eCRF as soon as possible after the participant's visit has been completed.

The participants will be advised to take prophylactic paracetamol 1 gm every 6 hours for 24 hours after vaccination.

The participant will be reminded to contact the site if there are any questions and to return to the clinic on Day 29.

Visit #3 (Day 29 [+14]): Blood collection and Second Vaccination:

Study participants will return for follow-up evaluations to the clinical study site 28 days following first vaccination. At this visit, investigator or delegate will perform the following procedures and evaluations in the following order:

1. Review and retrieval of diary card records till day 7 (reactogenicity cohort);
2. Assessment of any ongoing solicited AEs (note that all ongoing solicited AEs must be followed up by site staff until resolution) (reactogenicity cohort);
3. Medical interview of participant to assess any unsolicited AEs, SAEs since previous study visit;
4. Collection of concomitant medications and vaccinations history;
5. Targeted physical examination including assessment of vital signs.
6. A swab from nose and/or throat will be collected for RT-PCR testing for SARS-CoV-2 infection;
7. Collection of blood sample (approximately 10 mL) for immunological testing prior to second vaccination (immunogenicity cohort);
8. Additionally up to 20 ml blood sample will be collected from subset of 60 participants from immunogenicity cohort for assessment of CMI responses.
9. If the participant presents with any acute illness with or without fever on Day 29 then second vaccination will be delayed till the event is resolved.
10. In case of female participants of child bearing potential UPT will be performed prior to second vaccination. If UPT comes positive then the second dose of vaccine will not be administered;

Study Vaccination (Second dose)

The participant will receive second dose of 0.5 ml of either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 vaccine or Placebo as per the randomization schedule.

Post-Vaccination Activities

The participants will be observed closely for at least 30 minutes following vaccination, with appropriate medical treatment readily available in case of a rare anaphylactic reaction following the administration of vaccine. After 30 minutes (+30 minutes) post vaccination any solicited local and systemic AEs, any unsolicited AEs and Vitals (temperature, resting blood pressure, pulse and respiratory rate) will be recorded.

The participants in reactogenicity cohort will be issued a new diary card to record solicited adverse events for 7 days following second vaccination. The participants will be informed to visit the site on Day 57 and carry this completed diary at the time of visit.

The investigator or a delegate should ensure that all information are recorded in the source documents and accurately transcribed in the eCRF as soon as possible after the participant's visit has been completed.

The participants will be advised to take prophylactic paracetamol 1 gm every 6 hours for 24 hours after vaccination.

The participant will be reminded to contact the site in case of any questions and to return to the clinic on Day 57.

Occurrence of COVID-19 disease in between first and second dose: If the participant is confirmed with COVID-19 after the first dose but before the second dose, then the participant should be vaccinated with the second dose only two weeks after clinical recovery from COVID-19 disease. This is applicable, even if it is outside the recommended window period for the second dose. These participants will be continued in the study until Day 180 visit.

Visit # 4 (Day 57 [+14]): Blood collection

Study participants will return for follow-up evaluations to the study site 28 days following second vaccination. At this visit, investigator or delegate will perform the following procedures and evaluations in the following order:

1. Medical interview of participant to determine if any AEs occurred and if any concomitant medications or vaccines were taken/ received since the last study visit.)
2. Review and retrieval of diary card records till day 7 (reactogenicity cohort)
3. Assessment of any ongoing solicited AEs (note that all ongoing solicited AEs must be followed up by site staff until resolution) (reactogenicity cohort)
4. Check any ongoing AEs and concomitant medications since the last study visit (Visit 3) and record the resolution date (the end date), if available, in the source documents and eCRF.
5. Targeted physical examination including assessment of vital signs.

6. Collection of blood sample (approximately 10 mL) for immunological testing (immunogenicity cohort).
7. Additionally up to 20 ml blood sample will be collected from subset of 60 participants from immunogenicity cohort for assessment of CMI responses.

The investigator or a delegate should ensure that all information are recorded in the source documents and accurately transcribed in the eCRF as soon as possible after the participant's visit has been completed.

The participant will be reminded to contact the site in case of any questions and to return to the clinic on Day 180

Visit#5 (Day 90 [±14]): Telephonic contact

The study participants will be contacted by telephone to assess any SAEs that may have occurred since Day 57. They will also be reminded of the end of study visit at Day 180. SAEs, if any will be recorded and evaluated and participants will be advised for unscheduled visit to the site, if need be. Source records will be completed and all information will be recorded in the eCRF.

Visit#6 (Day 180 [+28]): End of study Visit

Study participants will return for follow-up evaluations to the clinical study site 179 days (approximately 6 months) following first vaccination. At this visit, investigator or delegate will perform the following procedures and evaluations in the following order:

1. Medical interview of participant if any SAEs occurred and if any concomitant medications or vaccines were taken/ received for treating the SAE since the last study visit.
2. Check any ongoing AEs and concomitant medications since the last study visit and record the resolution date (the end date), if available, in the source documents and eCRF.
3. Targeted physical examination including assessment of vital signs.
4. A swab from nose and/or throat will be collected for RT-PCR testing for SARS-CoV-2 infection

5. Collection of blood sample (approximately 10 mL) for immunological testing (immunogenicity cohort).
6. Additionally up to 20 ml blood sample will be collected from subset of 60 participants from immunogenicity cohort for assessment of CMI responses.

The investigator or a delegate should ensure that all information are recorded in the source documents and accurately transcribed in the eCRF as soon as possible after the participant's visit has been completed.

In case there are no ongoing SAEs, after this visit, the participation in the study will be completed. Source records will be completed and all information will be recorded in the eCRF (including "end of study" page).

Unscheduled Visits

Unscheduled visits may be performed at participant's requests or directly by the study site when the investigator or a delegate considers it necessary for diagnosis and/or management of a finding or AE. All unscheduled visits will be recorded in source and eCRF.

Unblinding procedure for Safety cohort in the light of Authorization for restricted use in emergency situation for COVISHIELD in India:

From an ethical standpoint and considering that the pandemic is still ongoing, if participants approach to the study team with a request for unblinding the site investigators' may carry out the unblinding.

Eligibility for unblinding:

The participant should be part of safety cohort and should have completed Day 90 telephonic contact (about two months post second dose) as per the study protocol and request the study team for unblinding.

Before unblinding, participants will be provided with information sheet to explain the entire process and written consent will be obtained about request for unblinding by the participant and willingness to receive the COVISHIELD offered by SII or any COVID-19 vaccine through the national programme.

After unblinding of the eligible participants:

- COVISHIELD group: No further action is required. These participants will be continued in the study as per protocol.
- Placebo group: If the participant is willing to receive COVISHIELD then it will be administered as per the recommended dose and schedule.

Even after unblinding, all study participants will be continued in the study for safety follow up till Day 180 as per study protocol.

Data collection post unblinding:

1. After unblinding, if a participant from the Placebo group receives one or both doses of COVID-19 vaccine, then this will be documented in the source and eCRF.
2. The safety data (only SAEs) from all such participants will be collected till Day 180 as per study protocol. In addition, any adverse events reported by the participants within 7 days post-vaccination will also be recorded. However, the data from the time of first dose of COVID-19 vaccine administration till Day 180 follow up will not be considered for control group analysis as they would no longer be part of the control group. Such data will be analysed separately in a descriptive manner.
3. Participants randomized to the COVISHIELD group will be continued in the study and followed for safety till Day 180 as per study protocol.

7.3 TESTING FOR COVID-19 DURING THE STUDY PERIOD:

If the participant presents with a new onset of fever (>38°C) OR cough OR shortness of breath OR anosmia/ageusia OR malaise OR fatigue OR history of contact with a confirmed COVID-19 positive case then a swab from nose and/or throat will be collected for PCR testing for SARS-CoV-2 infection.

At the COVID-19 testing visit, a swab from nose and/or throat, vital signs and other clinical data will be taken. Symptomatic cases will be managed as per national guidelines.

7.4 PARTICIPANT DISCONTINUATION

Participant discontinuation from study procedures prior to completion of the last study visit may occur for any of the following reasons:

- Dropout (defined as discontinuation initiated by a participant): Participation in the study is strictly voluntary. Participants have the right to withdraw their consent from study participation at any time and for any reason, without penalty. The participant may also initiate discontinuation due to an adverse event.
- Investigator-initiated: The study investigator may, at their discretion, discontinue a participant from the study if they consider it to be in the participant's best interest to do so (e.g., for safety concerns), or if the participant does not comply with the study requirements.
- Lost to follow-up: For participants who fail to attend scheduled visits, study staff are to make at least three attempts to contact the participant or participant's parent/guardian prior to considering the participant as lost to follow-up. These attempts should be recorded in the source documents.
- Sponsor-initiated: For example, if the sponsor is obliged to end the study for administrative or any other reasons.
- Ineligibility (either arising during the study or retrospectively, having been overlooked at screening).

Participants who discontinue prior to administration of the vaccine will be replaced, whereas those withdrawn after administration of the vaccine will not be replaced.

The reason for and date of participant discontinuation will be documented in the source documents and relevant electronic Case Report Form (eCRF). Before entering any category as the reason for the participant's discontinuation from the study, the investigator should make every effort to investigate whether an AE may have been related to the participant's discontinuation from the study. If an AE has been associated with the discontinuation, this must be described on the discontinuation eCRF page, even if it is not the primary reason for the participant's withdrawal. For participants considered lost to follow-up, the discontinuation date for the participant to be captured on the discontinuation eCRF page is the date of the participant's last completed study visit.

In the event of participant discontinuation from the study, reasonable efforts should be made to conduct the following procedures (unless participant consent to do so has been withdrawn):

- Review the solicited (and unsolicited) AE if still in use prior to discontinuation.

- Update any AE/SAEs that remained ongoing at the time of the participant's last visit prior to discontinuation.
- If within the protocol defined reporting period, collect any new AE/SAEs and concomitant medications since the participant's last visit and the time of discontinuation.
- If any new AE/SAEs reported since the participant's last visit and the time of discontinuation, perform a physical examination.
- Update participant contact information.

The sponsor or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. The study may be discontinued at one site or across multiple sites. If the clinical study is prematurely terminated at any of the site, the investigator of the respective site is to promptly inform the study participants and respective IEC and should assure appropriate therapy and follow up for the participants. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the sponsor.

7.5 MANAGEMENT OF PREGNANCY DURING STUDY

If a female participant becomes pregnant following administration of vaccine, she will be encouraged to complete remaining visits and study procedures unless medically contraindicated, and if possible and agreed to by the participant, she will continue to be followed for pregnancy outcome. The pregnancy and its outcome will be documented, even if birth occurs after the scheduled end of the study for the participant.

7.6 PRIOR AND CONCOMITANT THERAPY

7.6.1 Prior Medications and Vaccines

Any medications (including vaccines) that were administered to the participant within 30 days prior to the study vaccination will be considered as prior medications for this study. These will be recorded in the eCRF.

7.6.2 Concomitant Medications and Vaccines

At each study visit, the investigator/designee will ask the participants about any prescription or over-the-counter medication(s) taken since the last visit. Any medications taken at any time

during the study period must be recorded on source documents and the eCRF with trade and/or generic name, indication, dose, start and end dates.

Any treatments and/or medications specifically contraindicated, e.g., any investigational or non-registered product, any immunosuppressant and immune-modifying drug including systemic steroids, any immunoglobulin and blood product should be checked at each study visit subsequent to the study vaccination. If any become applicable during the study, it will not require withdrawal of the participant from the study but may determine a participant's evaluability in the per-protocol analysis.

Any vaccine not foreseen in the study protocol in the period starting at Visit 2 (Day 1) and ending at end of study visit must be recorded in the eCRF.

8. ASSESSMENTS OF IMMUNOGENICITY AND DISEASE INCIDENCE

Immunogenicity:

Immunogenicity will be assessed by IgG antibodies to SARS-CoV-2-Spike antigen by ELISA and virus/pseudovirus neutralising antibody assay.

Seroconversion is defined as four-fold increase in antibody titres from baseline.

Cell mediated immune responses will be assessed by flow cytometry based assays as an exploratory endpoint.

Immunogenicity testing will be performed at the PPD Richmond, VA, USA and ICMR - National AIDS Research Institute, Pune, India.

Incidence of COVID-19:

If the participant presents with a new onset of fever (≥38°C) OR cough OR shortness of breath OR anosmia/ageusia OR malaise OR fatigue OR history of contact with a confirmed COVID-19 positive case then a swab from nose and/or throat will be collected for PCR testing for SARS-CoV-2 infection. These samples will be processed for SARS CoV-2 RT-PCR testing. This process will be detailed in the laboratory manual.

All RT-PCR positive SARS CoV-2 cases (symptomatic as well as asymptomatic) from 15 days after each vaccination will be considered for analysis.

Severe COVID-19 disease will be defined as clinical signs of severe pneumonia or acute respiratory distress syndrome or sepsis or septic shock using clinical criteria and clinical

judgment. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate and other vital signs, need for ventilatory support, X-ray and CT scan imaging and blood test results, amongst other clinically relevant parameters.

9. METHODS FOR PROCESSING, LABEL AND STORAGE OF BLOOD SAMPLES

For all participants: At screening, approximately 1.5 ml blood sample will be collected for SARS-CoV-2 serology by IgG ELISA / CLIA or any other equivalent method.

For participants in immunogenicity cohort: Approximately 10 mL of blood will be drawn from participants in immunogenicity cohort at baseline, Day 29, Day 57 and Day 180. Additionally up to 20 ml blood sample will be collected from subset of 60 participants for assessment of CMI responses at baseline, Day 29, Day 57 and Day 180.

Not more than two attempts should be made to draw the required volume of blood.

The blood will be processed and aliquoted according to the Laboratory Manual. All aliquots will be stored at a temperature of -20°C or below. Each serum tube will be labeled with the labels provided by Sponsor/designee. Serum samples will be sent to the Sponsor or Sponsor designated laboratory.

Complete instructions for labeling and storage of serum samples will be provided in the Laboratory Manual.

10. ASSESSMENT OF SAFETY

10.1 SAFETY MONITORING

The Investigators at each study site will be responsible for continuous close safety monitoring of all study participants, and for alerting the protocol team if concerns arise. An internal team, the Protocol Safety Review (PSRT), will be set up to examine safety across the participating sites.

10.2 PROTOCOL SAFETY REVIEW TEAM

Safety will be monitored during the study by on-site clinical staff and routinely by the PSRT, an internal group of physicians which includes the ICMR Medical Officers, SIIPL Medical

Officers, a biostatistician and designated pharmacovigilance medical officer from the CRO. The PSRT may seek independent expert medical opinion as dictated by the occurrence of certain events. There will be periodic reviews of accruing safety data by the PSRT.

10.3 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a participant after administration of the vaccine and that does not necessarily have a causal relationship with the vaccine. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the vaccine, whether or not related to the vaccine. This definition includes exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the study are not considered AEs; however, these should be reported as part of the medical history at screening.

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

Solicited AEs are pre-specified local and systemic AEs that occur relatively more frequently or are known to be associated with immunization, which are monitored actively as potential indicators of vaccine reactogenicity. Investigators will not be required to assess causality of solicited AEs if the onset is during the solicitation period.

The following specific solicited adverse events will be monitored for this study:

Local reactions at injection site:

- Pain
- Tenderness
- Redness
- Warmth
- Itch
- Swelling
- Induration

Systemic reactions:

- Fever
- Chills
- Fatigue
- Malaise
- Headache
- Arthralgia

- Myalgia
- Nausea

Unsolicited AEs are any AEs reported spontaneously by the participant, observed by the study staff during study visits or those identified during review of medical records or source documents. Solicited AEs with an onset after the seven-day solicitation period will be considered unsolicited AEs.

10.4 SERIOUS ADVERSE EVENT (SAE)

An SAE is any AE that results in any of the following outcomes:

- Death
- Is life-threatening (i.e., the participant was, in the opinion of the investigator, at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or may require medical or surgical intervention to prevent one of the outcomes listed above

10.5 REPORTING PERIOD AND PARAMETER

Reactogenicity cohort:

Solicited AEs will be collected through 7 days following each vaccination using participant diary card. Solicited AEs with onset during the seven-day solicitation period that continue beyond the seven-day period will be reported as solicited AEs. Solicited AEs with onset after the seven-day solicitation period will be reported as unsolicited AEs.

All study participants:

Unsolicited AEs will be collected till 28 days following administration of each dose of study vaccine. SAEs will be collected following administration of the first dose of study vaccine until completion of the Visit 6 (Day 180) procedures.

Any untoward medical occurrence in a participant prior to administration of the vaccine but after signing the informed consent form, which is assessed by the investigator as being related to a study procedure, must also be documented and reported to the Sponsor.

10.6 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Confirmed COVID-19 cases throughout study duration following first dose of study vaccine will be captured in the source and eCRF. Hospitalization due to COVID-19 will be reported as SAE.

10.7 SEVERITY OF ADVERSE EVENTS

The grading scales cited below will be used to interpret the severity of each AE as such:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe (a severe AE is not necessarily an SAE, unless it meets one of the criteria that define an SAE; likewise, all SAEs are not necessarily by definition severe)

Grade 4 = Potentially Life-threatening (life-threatening AEs are to be reported as SAEs)

Grade 5 = Death

The severity of all AEs, listed specifically as an event in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1, July 2017, of the US National Institute of Health, will be assessed based on this Table, which is provided as Appendix V to this protocol and is currently also available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

The following grading scale should be used to grade the severity of all unsolicited AEs that are not listed as a specific event in the DAIDS Table cited:

Grade 1= Causes no or minimal interference with usual social & functional activities

Grade 2 = Causes greater than minimal interference with usual social & functional activities

Grade 3 = Causes inability to perform usual social & functional activities

Grade 4 = Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability

Grade 5 = Death

10.8 CAUSALITY OF ADVERSE EVENTS

The investigator will determine the causal relationship between the vaccine and the AE for all unsolicited AEs. The causality assessment is made based on the available information at the time of reporting and can subsequently be changed according to follow-up information. Causality determination is based on clinical assessment and should take into consideration the following factors:

- Is there a temporal relationship between the event and administration of the vaccine?
- Is there a plausible biological mechanism for the vaccine to cause the AE?
- Is there a possible alternative etiology for the AE, such as a concurrent illness or a concomitant medication?
- Are there previous reports of similar AEs associated with the vaccine or other vaccines in the same class?

For this study, the investigator must classify the causality of the AE according to the categories defined below:

Related: There is a reasonable possibility that the vaccine caused the event. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the vaccine and the AE.

Not Related: There is not a reasonable possibility that the administration of the vaccine caused the event.

In addition, related SAEs will be evaluated by the investigator for "expectedness" also. An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the IB or it is an event that is by nature more specific or more severe than a listed event.

10.9 FOLLOW-UP OF ADVERSE EVENTS

All AEs should be followed by the investigator or their designee until the event is resolved or determined to be irreversible, chronic, or stable by the investigator or participant is lost to follow up (including death). The investigator must ensure that any participants with AEs ongoing at study completion are advised or referred appropriately for continuation of care.

The outcome of an AE will be assessed as at the time of last observation per the following categories:

- Recovered/resolved without sequelae
- Recovered/resolved with sequelae
- Ongoing
- Death
- Unknown

10.10 GENERAL GUIDANCE ON REPORTING ADVERSE EVENTS

To improve the quality and precision of AE data, the investigator should observe the following guidelines:

- AEs must be graded, assessed for severity and causality, and reviewed by a site investigator.
- Whenever possible, use recognized medical terms when reporting AEs and avoid the use of colloquialisms or abbreviations.
- If known, report the diagnosis (i.e., syndrome or disease) rather than component symptoms, signs or laboratory values (e.g., report congestive heart failure rather than dyspnea, rales, and cyanosis); however, symptoms or signs that are considered unrelated to an observed syndrome or disease should be reported as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE).
- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A 'primary' AE, if clearly identifiable, generally represents the most accurate clinical term to report. For example: orthostatic hypotension $\rightarrow$ fainting and fall to floor $\rightarrow$ head trauma $\rightarrow$ neck pain; the primary AE is orthostatic hypotension, which is what should be reported. If a primary SAE is reported, events occurring secondary to the primary event should be described in the narrative description of the case.
- Death is an outcome of an event. The event that resulted in the death should be reported as the SAE.

- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.
- Elective surgical or diagnostic procedures with or without hospitalizations (e.g., circumcision or elective abortion of a pregnancy) will not be recorded as an AE. The procedure should be captured in the case narrative as part of medical history.
- A pregnancy in a participant is not in and of itself an AE.

10.11 REPORTING OF SAE

Any SAE occurring in a study participant during the study (after vaccine administration) must be reported. Information about all SAEs will be collected and recorded in SAE form. To ensure participant safety, each SAE must be reported by the Investigator to the Sponsor within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related.

The SAE form will always be completed as thoroughly as possible with all available details of the event. Even if the investigator does not have the entire recommended minimum information regarding a SAE, the SAE should still be submitted to sponsor, DCGI & respective IEC within 24 hours. Once additional relevant information is received, the SAE form should be updated. Reporting procedures will be followed as per the New Drugs and Clinical Trials Rules, 2019.

The investigator will always provide an assessment of causality at the time of the initial report.

Instructions for reporting of Serious Adverse Events

The recommended minimum information required for the initial SAE report is:

- Identifiable study participant
- A suspect medicinal product
- Identifiable reporting source
- An event or outcome that can be identified as SAE
- Preliminary causality assessment
- Severity

All SAEs are also to be documented on the Adverse Events eCRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate eCRF pages in addition to the grading and outcome of the AE.

Contact Persons and Numbers

The details of the Sponsor's contact person for safety reporting or questions are listed below and will also be kept on-site in the Investigator File.

[redacted]

Follow-up of SAEs

After receipt of the initial report, sponsor/designee may contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be documented and followed up until the event has resolved, subsided, stabilized, disappeared or is otherwise explained. All follow-up activities have to be reported, if necessary on one or more consecutive SAE report forms in a timely manner.

10.12 TREATMENT OF AE AND SAES

Treatment of any AE and SAE is at the sole discretion of the investigator and according to current Good Medical Practice. The applied measures should be recorded in eCRF.

Cost of the medical care for vaccine related AEs will be borne by the sponsor.

11. STATISTICAL CONSIDERATIONS

11.1 OVERVIEW AND GENERAL CONSIDERATIONS

This is a Phase 2/3, observer-blind, randomised, controlled study in healthy adults aged ≥ 18 years in India, for comparison of the safety of COVISHIELD with Oxford/AZ-ChAdOx1 nCoV-19 and Placebo, and immunogenicity with Oxford/AZ-ChAdOx1 nCoV-19 in prevention of SARS CoV-2 infection.

A detailed statistical analysis plan for preparation of the final study report will be created and finalized prior to database lock. All statistical analyses will be performed using SAS® software Version 9.4 or later.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0 or later). The frequency count and percentage of participants will be summarized by system organ class and preferred term. Study participant-wise data listing will be provided.

The non-inferiority test will be performed using a one-sided significance level of 2.5%. Any other statistical tests will be performed using a two-sided significance level of 5%. For consistency two-sided 95% confidence intervals (CIs) will be provided throughout. The main purpose of the safety analysis is to estimate the incidence rate of different events in each vaccine group and their difference between vaccine groups. Whilst the intention is not to show a difference between vaccine groups, p-values corresponding to CIs will also be calculated and shown for illustrative purposes. No statistical tests will be performed at any interim analyses of safety data.

11.2 RANDOMIZATION

The randomization scheme for treatment assignment (vaccine groups) will be generated and maintained by independent personnel at PPD. PPD biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary,

North Carolina) for IRT, which will link sequential participant randomization numbers to treatment codes.

The eligible participants will be enrolled and randomized in the study online through IRT. Each participant enrolled into the study will be assigned a randomization number to assign vaccine group after identification and eligibility data have been entered into the IRT system.

A total of 1600 eligible participants of ≥ 18 years of age will be enrolled the study. Of these 400 participants will be part of immunogenicity cohort and will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 vaccine, respectively. The remaining 1200 participants from safety cohort will be randomly assigned in a 3:1 ratio to receive either COVISHIELD or Placebo, respectively.

Eligible participants will receive 0.5 ml of either COVISHIELD or Oxford/AZ-ChAdOx1 nCoV-19 vaccine or Placebo on Day 1 and Day 29 as per randomization.

11.3 SAMPLE SIZE AND POWER

The study is designed to have a 95% probability to detect at least one causally related serious adverse event among 1200participants administered COVISHIELD, if the frequency of causally related serious adverse events is 1/400.

It is planned to randomize 400 participants for the immunogenicity analysis for the study (300 to COVISHIELD and 100 to Oxford/AZ-ChAdOx1 nCoV-19 vaccine). Assuming that the proportion of non-evaluable participants ≤ 21% (which leads to a sample size of 316 evaluable participants), the study will have at least 90% power to show non-inferiority of immune responses assuming a Coefficient of Variation of 1.2 (which was estimated based on natural log-transformed IgG antibody titers against SARS-CoV-2 spike protein from the interim analysis of the phase 1/2 study of Oxford/AZ-ChAdOx1 nCoV-19 vaccine (Refer Investigator's Brochure). Non-inferiority will be concluded if the lower limit of the 95% CI for the GMT ratio for IgG antibodies against SARS-CoV-2 spike protein between COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccine is > 0.67. Additional assumptions include a one-sided significance level of 0.025 and '0' difference in IgG antibody titers against SARS-CoV-2 spike protein between the two vaccine groups (i.e. a GMT ratio between both vaccine groups of 1). Sample size calculations were performed using a Non-inferiority test for the ratio of two means in PASS 15.0.7 Version software.

The following table shows the evaluable sample size to demonstrate non-inferiority of immune response:

Power (%)	Evaluable sample size (SS)			% Non-evaluable participants (Dropout rate)
	Total number of participants	COVISHIELD	Oxford/AZ-ChAdOx1 nCoV-19	
90	316	237	79	21%

11.4 ANALYSIS POPULATIONS

11.4.1 Enrolled Population

All participants who provide written informed consent, regardless of the participants screening, randomization and treatment status in the study.

11.4.2 Full Analysis Population

All participants in the Enrolled population who received any vaccination and provided an evaluable serum sample post vaccination. Participants in the Full Analysis population will be analyzed 'as randomized', i.e., according to the vaccine a participant was designated to receive, which may be different from the vaccine the participants actually received.

11.4.3 Safety Population

All participants in the Enrolled population who received any vaccination. All safety analyses will be performed using this population. Participants in the safety population will be analyzed as 'treated' (i.e. actual vaccine received).

11.4.4 Immunogenicity Population

Immunogenicity Analysis population will be a subset of Full Analysis population. Immunogenicity Analysis population consist of all participants who received any study vaccination, excluding any data from time points following a SARS-CoV-2 infection or major protocol deviation (defined as having missed 2nd Vaccination or use of an immunosuppressant, immune-modulating medication or vaccines which interfere with assessing immunogenicity). All immunogenicity analyses will be performed using this population. Participants in the immunogenicity population will be analyzed as 'treated' (i.e. actual vaccine received).

11.5 ANALYSIS PLAN

11.5.1 Intercurrent events (IcEv)

Label	Intercurrent Event Type
IcEv1 (Death)	Death due to any cause; this is an IcEv because it leads to the endpoint (e.g. antibody titer) not existing at later timepoints.
IcEv2 (Immune modifiers)	Use of Immunosuppressant and Immune modifying medications or vaccines which interfere with assessing immunogenicity.
IcEv3 (COVID-19/SARS-CoV-2 infection)	Incidence of COVID-19/SARS-CoV-2 infection after vaccination.
IcEv4 (Missed 2nd dose of vaccine)	Does not receive the second scheduled vaccine at Day 29

11.5.2 Estimand Specifications;

Attributes for the primary safety estimand with strategies for IcEvs are presented in the Table 11.5.2.1.

Table 11.5.2.1 Primary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To assess the safety of COVISHIELD vaccine.
Estimand Label	Estimand 1
Estimand Description	Proportion of participants with at least one causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination. A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination Infections and death (meeting criteria) are included in the endpoint (composite strategy).
Target Population	Vaccinated healthy individuals aged 18 years and older
Endpoint	Occurrence of causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination.
Treatment Condition(s)	Test: COVISHIELD Vaccine
Population-Level Summary	Proportion of participants with causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination.
Intercurrent Event Strategy	
IcEv1 (Death)	Composite – will be included as related SAEs (if meeting criteria)
IcEv2 (Immune modifiers)	Treatment policy – i.e. included, irrespective use of Immune modifiers.
IcEv3 (COVID-19/SARS-CoV-2 infection)	Composite as per normal practice- COVID-19/SARS-CoV-2 infection during the course of the study maybe part of the endpoint depending on nature of infection.
IcEv4 (Missed 2nd Dose of Vaccine)	Treatment policy – assessed irrespective of whether 2nd vaccination received
Rationale for Strategies	Deaths and infections during study would contribute as part of the endpoint (if in time window of interest and meeting criteria). A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications (we cannot exclude the safety events even subject receive the immune modifier) or missed 2nd vaccination.

Refer to Section 11.5.1 specific numbered intercurrent event definitions.

Table 11.5.2.2 Co-Primary Immunogenicity Objectives and Estimands with Rationale for Strategies to Address Intercurrent Events

Objective	To assess immunogenicity of COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA assay.
Estimand Label	Estimand 2
Estimand Description	Ratio of geometric mean titres (GMTs) of IgG antibodies against SARS-CoV-2 spike protein in healthy individuals at Visit 4 – Day 57 (+14) after second vaccination between vaccines (COVISHIELD/ Oxford/AZ-ChAdOx1 nCoV-19). Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines or missed 2nd vaccine or death.
Target Population	Vaccinated healthy individuals.
Endpoint	IgG antibodies against SARS-CoV-2 spike protein at Visit 4 – Day 57 (+14) after second vaccination.
Treatment Condition(s)	COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccines
Population-Level Summary	GMT ratio between vaccinations (test/reference)
Intercurrent Event Strategy	
IcEv1 (Death)	Hypothetical strategy
IcEv2 (Immune modifiers)	Hypothetical strategy
IcEv3 (COVID-19/SARS-CoV-2 infection)	Hypothetical strategy
IcEv4 (Missed 2nd Dose of Vaccine)	Hypothetical strategy as interested in antibody levels had the 2nd vaccination been received per schedule.
Rationale for Strategies	The hypothetical strategy is used to estimate effect attributable to the difference in vaccines without any use of immune-modifying medications or other vaccinations and without influence from subsequent infection, missed 2nd vaccine and death.

Refer to Section 11.5.1 specific numbered intercurrent event definitions.

Table 11.5.2.3 Secondary Safety Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To assess the safety, tolerability and reactogenicity profile of the COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine and Placebo vaccine.	
Estimand Label	Estimand 3	Estimand 4
Estimand Description	Proportion participants at least one SAEs, and proportion with at least one Unsolicited AEs • Up to Visit 6 – Day 180 (+28) following first vaccination with SAE • Within 28 days following each vaccination with Unsolicited AEs. A treatment policy strategy is used for assessing safety irrespective of use of immune modifying medications or other vaccinations and missed 2nd dose of vaccine. Infections and death are included in the endpoint (composite strategy).	Proportion participants at least one solicited local and/or systemic adverse events (AEs) • Within 7 days following each vaccination. A treatment policy strategy is used for assessing safety irrespective of use of modifying medications and to assess missed 2nd vaccine dose. composite strategy is used to understand safety without subsequent infection. While on treatment strategy is used to utilize all available data until event.
Target Population	Vaccinated healthy individuals aged 18 years and older	Vaccinated healthy individuals aged 18 years and older.
Endpoint	• Occurrence of SAEs Up to Visit 6 – Day 180 (+28) following first vaccination. • Occurrence Unsolicited AEs for 28 days following each vaccination.	• Occurrence of solicited local and/or systemic adverse events (AEs) for 7 days following each vaccination (Reactogenicity cohort)
Treatment Condition(s)	COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo Vaccine.	COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 Vaccine.
Population-Level Summary	Proportion	Proportion
Intercurrent Event Strategy		
IcEv1 (Death)	Composite strategy	While on treatment strategy (data until death is utilized)
IcEv2 (Immune modifiers)	Treatment policy	Treatment policy
IcEv3 (COVID-19/SARS-CoV-2 infection)	Composite strategy	Composite strategy
IcEv4 (Missed 2nd Dose of Vaccine)	Treatment policy –If subject missed second dose of vaccine then AEs data post second vaccination will not be used in the analysis	Treatment policy –If subject missed second dose of vaccine then AEs data post second vaccination will not be used in the analysis
Rationale for Strategies	A treatment policy strategy is used for assessing safety irrespective of use of Immune modifiers (we cannot exclude the safety events even subject receive the immune modifier). Infections and death (if they meet the AE and time window criteria) are included in the endpoint (composite strategy).	A treatment policy strategy is used for assessing safety irrespective of use of Immune modifiers (we cannot exclude the safety events even subject receive the immune modifier). Composite treatment strategy is used to understand safety without subsequent infection. While on treatment policy is used to utilize the data until death

Refer to Section 11.5.1 specific numbered intercurrent event definitions.

Table 11.5.2.4 Secondary Immunogenicity Objectives and Estimands with Rationale for Strategies to Address Intercurrent Events

Objective	To assess immunogenicity of the COVISHIELD vaccine in comparison with the Oxford/AZ-ChAdOx1 nCoV-19 vaccine by IgG ELISA and neutralizing antibody assays.	
Estimand Label	Estimand 5	Estimand 6
Estimand Description	GMTs of Nab at Baseline and Visit 4 – Day 57 (+14) and GMTs of IgG antibodies against SARS-CoV-2 spike protein at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death.	Proportion of participants with seroconversion for virus neutralizing antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and proportion with seroconversion for SARS-CoV-2 spike protein IgG at Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death.
Target Population	Vaccinated healthy individuals aged 18 years and older.	Vaccinated healthy individuals aged 18 years and older.
Endpoint	• NAb against SARS-CoV-2 spike protein at Baseline and Day 57. • IgG antibodies against SARS-CoV-2 spike protein at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28)	• Seroconversion for NAb using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) • Seroconversion for SARS-CoV-2 spike protein IgG at Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28)
Treatment Condition(s)	COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccine	COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccine
Population-Level Summary	GMT ratio between vaccinations (ChAdOx1 nCoV-19 / Oxford/AZ-ChAdOx1 nCoV-19)	Proportion of participants with seroconversion in COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19
Intercurrent Event Strategy		
IcEv1 (Death)	Hypothetical	Hypothetical
IcEv2 (Immune modifiers)	Hypothetical	Hypothetical
IcEv3 (COVID-19/SARS-CoV-2 infection)	Hypothetical.	Hypothetical
IcEv4 (Missed 2nd Dose of Vaccine)	Hypothetical.	Hypothetical
Rationale for Strategies	Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection and immune-modifying medications.	Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection and immune-modifying medications.

Refer to Section 11.5.1 specific numbered intercurrent event definitions.

Table 11.5.2.5 Secondary Objective(s) of Incidence of COVID-19 and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	• To compare the incidence of symptomatic COVID-19 disease between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. • To compare the incidence SARS-CoV-2 infection between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. • To compare the incidence of severe COVID-19 between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine.
Estimand Label	Estimand 7
Estimand Description	Proportion of participants with incidence of confirmed (RT-PCR positive) symptomatic cases of COVID-19, virologically confirmed (RT-PCR positive) cases of COVID-19, Hospitalizations due to COVID-19, Severe COVID-19 infection, Intensive care unit (ICU) admissions associated with COVID-19 and Deaths associated with COVID-19 from post 14 days post-vaccination until the end of the study visit 6 – Day 180 (+28). A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination Infections and death (meeting criteria) are included in the endpoint (composite strategy).
Target Population	Vaccinated participants who do not have an active or prior infection at vaccination
Endpoint	• Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Virologically confirmed (RT-PCR positive) cases of SARS-CoV-which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Hospitalizations due to COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Severe COVID-19 infection which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Intensive care unit (ICU) admissions associated with COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28). • Deaths associated with COVID-19 which occur 14 days after each vaccination until the end of the study Visit 6 -day 180 (+28).
Treatment Condition(s)	COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo Vaccine.
Population-Level Summary	Proportions of COVID -19 incidence [defined in the endpoint in COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo]
Intercurrent Event Strategy	
IcEv1 (Death)	Composite (meeting criteria of COVID 19)
IcEv2 (Immune modifiers)	Treatment policy
IcEv3 (COVID-19/SARS-CoV-2 infection)	Composite
IcEv4 (Missed 2nd Dose of Vaccine)	Treatment policy

Objective	• To compare the incidence of symptomatic COVID-19 disease between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. • To compare the incidence SARS-CoV-2 infection between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine. • To compare the incidence of severe COVID-19 between COVISHIELD, Oxford/AZ-ChAdOx1 nCoV-19 and Placebo vaccine.
Estimand Label	Estimand 7
Rationale for Strategies	A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination. Infections and death (meeting criteria) are included in the endpoint (composite strategy).

Refer to Section 11.5.1 specific numbered intercurrent event definitions.

Estimand strategies for Estimand 8 and 9 are same as that of the Estimand 5 and 6 respectively.

11.5.3 Table of statistical method and sensitivity analysis -

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 1 (Primary)	Proportion of participants with at least one causally related SAEs • Up to Visit 3 – Day 29 (+14) following first vaccination • Up to Visit 4 – Day 57 (+14) following first vaccination. • Up to Visit 6 – Day 180 (+28) following first vaccination. A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination Infections and death (meeting criteria) are included in the endpoint (composite strategy).	Safety Analysis Population	Infections and death (meeting criteria) are included in the endpoint (composite strategy).	Frequencies and estimate of the proportion of participants with at least one causally related serious adverse events (SAEs) throughout the study duration following the study vaccination will be computed by vaccine group using two sided 95% Clopper-Pearson confidence intervals.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 2 (Co-Primary)	Ratio of geometric mean titres (GMTs) of IgG antibodies against SARS-CoV-2 spike protein in healthy individuals at Visit 4 – Day 57 (+14) after second vaccination between vaccines (COVISHIELD/ Oxford/AZ-ChAdOx1 nCoV-19). Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines or missed 2nd vaccine or death. Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines or missed 2nd vaccine or death.	Immunogenicity Analysis Population	Values below the limit of quantification (LOQ) or limit of detection (LOD) will be replaced by LOQ/2 and LOD/2, respectively. Multiple imputation of missing values (and those removed from IA population) assumed to MAR.	ANCOVA will be fitted to the log transformed IgG antibodies against SARS-CoV-2 spike protein with terms for vaccine group, log baseline titer, age group and sex. Individual mean and 95% CI values by treatment from this model will be used to generate the geometric mean titers with 95% CI at each time point and geometric mean ratio (GMR) with 95% CI at Visit 4 – Day 57 (+14) after second vaccination by back transforming to the original scale. Hypothesis testing H0: GMTSII/GMTOXF ≤ 0.67 (Inferior) H1: GMTSII/GMTOXF > 0.67 (Non-Inferior) Where – SII- COVISHIELD and OXF-Oxford/AZ-ChAdOx1 nCoV-19 The lower limit of the 95% CI for the GMR will be compared with a non-inferiority margin of 0.67 and COVISHIELD vaccine will be declared non-inferior to Oxford/AZ-ChAdOx1 nCoV-19 if > 0.67.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 3	Proportion participants at least one SAEs, and proportion with at least one Unsolicited AEs • Up to Visit 6 – Day 180 (+28) following first vaccination with SAE • Within 28 days following each vaccination with Unsolicited AEs. A treatment policy strategy is used for assessing safety irrespective of use of immune modifying medications or other vaccinations and missed 2nd dose of vaccine. Infections and death are included in the endpoint (composite strategy).	Safety Analysis Population	None	Frequencies and estimate of the proportion of participants with at least one serious adverse events (SAEs) throughout the study duration following the study vaccination and proportion of participants with at least one unsolicited AEs for 28 days following each vaccination will be computed by vaccine group using two sided 95% Clopper-Pearson confidence intervals. The difference between the vaccines (COVISHIELD - Oxford/AZ-ChAdOx1 nCoV-19) and (COVISHIELD - Placebo) in the proportion of the participants with at least one serious adverse events throughout the study duration following the study vaccination and proportion of participants with at least one unsolicited AEs for 28 days following each vaccination will be provided along with their two-sided 95% CIs obtained by the Miettinen and Nurminen method.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 4	Proportion participants at least one solicited local and/or systemic adverse events (AEs) • Within 7 days following each vaccination. A treatment policy strategy is used for assessing safety irrespective of use of modifying medications and to assess missed 2nd vaccine dose. composite strategy is used to understand safety without subsequent infection. While on treatment strategy is used to utilize all available data until event.	Safety Analysis Population (Reactogenicity cohort)	None	Frequencies and estimate of the proportion of participants with at least one solicited local and systemic adverse events (AEs) for 7 days following each vaccination will be computed by vaccine group using two sided 95% Clopper-Pearson confidence intervals. The difference between the vaccines (COVISHIELD - Oxford/AZ-ChAdOx1 nCoV-19) in the proportion of the participants with at least one solicited local and systemic adverse events (AEs) for 7 days following each vaccination will be provided along with their two-sided 95% CIs obtained by the Miettinen and Nurminen method.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 5	GMTs of Nab at Baseline and Visit 4 – Day 57 (+14) and GMTs of IgG antibodies against SARS-CoV-2 spike protein at Baseline, Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death.	Immunogenicity Analysis Population	Values below the limit of quantification (LOQ) or limit of detection (LOD) will be replaced by LOQ/2 and LOD/2, respectively.	MMRM will be fitted to the log transformed titer values of NAb and IgG antibodies against SARS-CoV-2 with terms for vaccine group, log baseline titer, visit, age group and sex with interactions for treatment by visit. The repeated timepoints on subject will be modelled (Details of the covariance structure will be provided in the SAP). Individual mean and 95% CI values by treatment from this model will be used to generate the geometric mean titers with 95% CI at each time point and GMRs with 95% CIs at each time point by back transforming to the original scale	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 6	Proportion of participants with seroconversion for virus neutralizing antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and proportion with seroconversion for SARS-CoV-2 spike protein IgG at Visit 3 – Day 29 (+14), Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death.	Immunogenicity Analysis Population	Rules for determination of seroconversion status for participants with missing values (and those removed from IA population) will be described in the SAP.	Summary of the number of participants with missing measurement, proportion of participant with seroconversion and associated confidence intervals will be summarized by vaccine group and visit for NAb using live and/or pseudotype SARS-Cov-2 and SARS-CoV-2 spike protein IgG. The proportion participant with seroconversion for NAb using live and/or pseudotype SARS-Cov-2 SARS-CoV-2 spike protein IgG at each post baseline visit will be analyzed using a logistic regression model with the treatment group as factor and baseline titer value and age group (18-59 years and ≥ 60) as covariate. Estimate of the odds ratio along with associated 95% Wald confidence interval and two-sided p-values will be presented for the comparison between COVISHIELD and Oxford/AZ-ChAdOx1 nCoV-19 vaccine.	Supplementary: Similar repeat analysis based on Full Analysis population will be provided.

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 7	Proportion of participants with incidence of confirmed (RT-PCR positive) symptomatic cases of COVID-19, virologically confirmed (RT-PCR positive) cases of COVID-19, Severe COVID-19 infection, Intensive care unit (ICU) admissions associated with COVID-19, Hospitalizations due to COVID-19 and Deaths associated with COVID-19 from post 14 days post-vaccination until the end of the study visit 6 – Day 180 (+28). A treatment policy strategy is used for assessing safety irrespective of use of immune-modifying medications/vaccinations or missed 2nd vaccination. Infections and death (meeting criteria) are included in the endpoint (composite strategy).	Safety Analysis Population		Proportion participants with incidence of confirmed (RT-PCR positive) symptomatic cases of COVID-19, virologically confirmed (RT-PCR positive) cases of COVID-19, Severe COVID-19 infection, Intensive care unit (ICU) admissions associated with COVID-19, Hospitalizations due to COVID-19 and Deaths associated with COVID-19 which occur 14 days after each vaccination until the end of the study visit 6 – Day 180 (+28) will be computed by vaccine group using two sided 95% Clopper-Pearson confidence intervals. The difference in percentages between the vaccines (COVISHIELD - Oxford/AZ-ChAdOx1 nCoV-19) and (COVISHIELD - Placebo) will be provided along with their two-sided 95% CIs obtained by the Miettinen and Nurminen method.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/ Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity Analysis**
Estimand 8	GMTs of NAb at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28) Hypothetical strategy is used to understand antibody levels achieved through vaccination, without subsequent COVID-19/SARS-CoV-2 infection or use of any immune-modifying medications or other vaccines missed 2nd vaccine and death. **Endpoints** • NAb against SARS-CoV-2 spike protein at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28).	Immunogenicity Analysis Population	Values below the limit of quantification (LOQ) or limit of detection (LOD) will be replaced by LOQ/2 and LOD/2, respectively.	MMRM as per Estimand 5	
Estimand 9	Proportion of participants with seroconversion for virus neutralizing antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28). [Same hypothetical strategies as for Estimand 6] **Endpoints** • Seroconversion for NAb using live and/or pseudotype SARS-CoV-2 virus at Visit 4 – Day 57 (+14) and Visit 6 – Day 180 (+28).	Immunogenicity Analysis Population	Rules for determination of seroconversion status for participants with missing values (and those removed from IA population) will be described in the SAP.	Logistic regression as per Estimand 6	Supplementary: Similar repeat analysis based on Full Analysis population will be provided.

The details about analysis regarding cell mediated immune responses will be defined in the SAP.

Two interim analyses are planned as below:

1. Safety data of 28 days post second vaccination (Day 57) of all study participants.
2. Immunogenicity data by IgG ELISA at 28 days post second vaccination (Day 57) of participants in immunogenicity cohort and safety data of 28 days post second vaccination (Day 57) of all study participants

11.5.4 Analysis of Demographic and Baseline Characteristics

Demographic (age, gender, height, weight) and baseline characteristics (medical history, Pre-existing conditions, and Prior medications) will be presented descriptively by vaccine group.

The quantitative variables will be summarized as mean, standard deviation, median, minimum and maximum and categorical variables will be summarized as frequency and percentage. Distributions of participants by gender, and age group will be summarized as frequency and percentages by overall and by vaccine group.

Baseline characteristics such as medical history, pre-existing conditions will be tabulated by vaccine group using MedDRA dictionary classification and prior and concomitant medications will be tabulated by vaccine group using WHODD drug classification.

11.5.5 Statistical Methods for Primary and Co-Primary Objective

Statistical Method for the Primary endpoint

A summary of the statistical methods for primary objective (Estimand 1) is presented in the section 11.5.3 of the protocol.

Summaries of the number of participants (%) with at least one causally related serious adverse events (SAEs) throughout the study duration will be presented.

The number of events leading to a participant not proceeding with the second vaccination will also be summarized.

Statistical Method for the Co-Primary endpoint

A summary of the statistical methods for the Co- primary objective (Estimand 2) is presented in the section 11.5.3 of the protocol.

To assess the Co-primary objectives, the following non-inferiority hypotheses will be tested on the GMT for of antibodies measured by SARS-CoV-2 spike protein IgG on Visit 4 - Day 57 (+14) post second vaccination.

Hypothesis testing:

H_0: $GMT_{SII}/GMT_{OXF} \leq 0.67$ (Inferior)

H_1: $GMT_{SII}/GMT_{OXF} > 0.67$ (Non-Inferior)

Where – SII- COVISHIELD and OXF- Oxford-ChAdOx1 nCoV-19

The lower limit of the 95% CI will be compared with non-inferiority margin of 0.67 and COVISHIELD will be declared non-inferior to Oxford/AZ-ChAdOx1 nCoV-19 if > 0.67.

11.5.6 Statistical Methods for Secondary and Exploratory Objectives

Immunogenicity analysis of virus neutralising antibodies (NAb) using live and/or pseudotype SARS-CoV-2 virus and IgG antibodies against SARS-CoV-2 spike protein;

A summary of the statistical methods and sensitivity analysis for the immunogenicity objective (Estimand 5, 6, 8 and 9) is presented in the section 11.5.3 of the protocol.

Seroconversion is defined as four-fold increase in antibody titres from baseline.

Summary of the number of participants with missing measurement, proportion of participant with seroconversion and associated confidence intervals will be summarized by vaccine group. In addition to the proposed analysis in section 11.5.3, the GMTs and GMFRs from baseline will be summarized with descriptive statistics including a boxplot (on log scale) versus time.

Analysis of Incidence of COVID-19 –

A summary of the statistical methods for the analysis secondary objective of COVID (Estimand 7) is presented in the section 11.5.3 of the protocol.

In addition to the proposed analysis summary of Frequencies and percentage of participants with confirmed (RT-PCR positive) symptomatic cases of COVID-19, virologically confirmed (RT-PCR positive) cases of SARS-CoV-2, Severe COVID-19 infection, Intensive care unit (ICU) admissions associated with COVID-19, Hospitalizations due to COVID-19 and Deaths associated with COVID-19 which occur 14 days after each vaccination until the end of the study visit 6 – Day 180 (+28) will be presented for both vaccine group and overall.

11.5.6.1 Safety Objectives

11.5.6.1.1 Analysis of Solicited and Unsolicited Adverse Events

A summary of the statistical methods for the analysis relating secondary objective of safety, tolerability and reactogenicity profile (Estimand 3 and 4) is presented in Section 11.5.3 of the protocol.

In addition to above proposed analysis, the following summaries will be provided.

All solicited AEs will be summarized according to defined severity grading scales. Frequencies and percentages of participants experiencing each AE will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic AE overall will also be presented.

Solicited adverse events reported until 7 days post-vaccination from first and second dose will be summarized by maximal severity and by vaccine group. Separate analysis will be performed for solicited AEs reported 30 minutes after vaccination. All the solicited reaction occurring up to 7 days after each vaccination will be summarized according to severity grading.

All unsolicited AEs occurring during the study, assessed either as related or not related to vaccine by the investigator, will be recorded. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to PTs using MedDRA. The AEs will then be grouped by MedDRA PTs into frequency tables according to SOC. All reported AEs, as well as AEs assessed by the investigator as related to vaccine, will be summarized according to SOC, PT within SOC, and severity.

Safety and tolerability of study vaccines will be evaluated using the following endpoints:

- Number and severity of solicited local and systemic adverse events (AEs) and relatedness of all solicited systemic adverse events during the first 7 days after each vaccination
- Number, severity and relatedness of all unsolicited AEs and SAEs through the 28 days after each vaccination
- Number, severity and relatedness of all SAEs through the entire study period up to Visit 6 i.e. Day 180 visit

Generally, safety evaluations will be descriptive in nature, and observed differences will be evaluated for medical relevance. Tabular summaries of safety data will be provided for each vaccine group.

Occurrence of local and systemic reactogenicity within 7 days after each vaccination, as well as AEs up to 28 days after each vaccination and SAEs during the entire study period, will be

reported for all vaccine groups. Proportions of severe (Grade >= 3) reactions and classes of AEs of interest (at least one AE) will be compared.

Data listings of all adverse events will be provided by participant.
Additional details of the safety analysis such as (vital, physical examination. Etc.), disposition demographic will be provided in the statistical analysis plan.

11.5.7 Handling of Dropouts and Missing Data

Details for the imputation of missing values are outlined in Section 11.5.3; further details will be document in the SAP.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 PRE-STUDY DOCUMENTATION

Prior to enrolment of participants at the study site, specific regulatory documents must be available, such as regulatory (DCGI) and Institutional Ethics Committee (IECs) approvals; curriculum vitae for investigator and study staff; standard operating procedures (SOPs) and other essential documents. Sponsor/designee will inform the investigator which documents need to be provided according to the applicable regulatory requirements.

12.2 MONITORING

Sponsor monitoring responsibilities will be provided through qualified and appropriately trained individuals designated by CRO to carefully monitor all aspects of the study. A site initiation visit will be conducted prior to the beginning of the study and monitoring will be conducted during and at closeout of the study by the study monitor.

During the course of the study, the monitors will visit the clinical sites at intervals in order to verify that:

- The data are authentic, accurate and complete
- The safety and rights of participants are being protected
- The study is conducted in accordance with the approved protocol (and any subsequent amendment), GCP and all applicable regulatory requirements

Monitors will periodically contact the site and perform site visits. The extent, nature and frequency of site visits will be decided before the start of the study and will be based on

considerations as study objectives, study design and complexity, and enrolment rate. During these contacts, the monitor will:

- Check and assess the progress of the study
- Review study data collected
- Perform source data verification, identify any issues and address their resolution

Monitoring will be conducted according to ICH-GCP. The individuals responsible for monitoring the study will have access to all records necessary to ensure the integrity/validity of the recorded data and will periodically review the progress of the study.

The investigator must agree to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

The monitor must contact the site prior to the start of the study to discuss the protocol and data collection procedures with the site personnel.

The investigator should allow representatives of the Ethics Committee, Regulatory Authority and the sponsor to visit the study site.

12.3 DATA MANAGEMENT AND PROCESSING

Site PI is responsible for ensuring timely completeness and accuracy of data reported. Data collection is the responsibility of clinical trial staff at the study site under supervision of site PI. The CRO is responsible for clinical data management activities, including quality review, analysis and reporting of study data according to SOPs.

Data Collection

Data will be entered electronically by site study staff using Internet in eCRF. The data system will include password protection. Instructions for use of the system will be included in eCRF manual.

Clinical data will be entered directly from source documents. All source documents should be completed in neat and legible manner to ensure accurate interpretation of data. All information required by the study protocol must be entered into eCRF. An explanation must be provided for any missing data. Source documentation supporting the eCRF data should document the dates and details of study procedures, AEs and participant status. PI/site staff will maintain

information in eCRFs and all source documents that support the data collected from each participant.

Study monitor will check for completeness and accuracy of eCRF during the monitoring visits.

Data Management Procedures

Site staff should complete eCRFs as soon as possible after the information is collected. Completed eCRFs must be submitted for each screened participant who signs the study specific ICF.

Internal data quality checks such as automatic range checks, checks to identify data that appear inconsistent, incomplete or inaccurate will be programmed into eCRF that will help in real time review of data, as and when, clinical data is entered into the system by site staff.

Clinical Data Management team at CRO will review the data for quality and will provide several quality assurance reports to ensure that study data is clean and complete. Quality assurance reports will include, but are not limited to, the following: missing forms, automated and manual data queries. Data queries will be distributed to the sites at scheduled time period for site staff to review and update the database.

Coding

All medical verbatim terms will be coded by Clinical Data Management and reviewed by a medical doctor according to most recent versions of MedDRA (Adverse events and medical history) and the WHO Drug Dictionary enhanced version (concomitant medication).

Database Lock Procedures

Database will be locked upon completion of the following activities:

- All participants have completed the follow up visits
- All the participant data has been entered in the database
- All data anomalies have been resolved
- Study monitoring has been completed
- All listings of the database have been reviewed and discussed for assessment of consistency and medical plausibility.

Procedures for Analysis

Data will be analyzed as per the **pre-specified Statistical Analysis Plan (SAP)** after the database lock**.** An audit trail will be kept of any subsequent changes to the data.

12.4 STUDY AND SITE CLOSURE

Upon completion of the study, the monitor and the investigator will conduct the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation and return to sponsor or destruction at sites of used and unused vaccines
- Review of site study records for completeness
- Return of all study data to Sponsors or designee.

Sponsors reserve the right to temporarily suspend or prematurely discontinue this study at either a single site or at all sites at any time for any other reason.

If the study is stopped or suspended prematurely, Sponsor will inform the investigator(s) as well as the regulatory authorities about the decision and the reasons for termination or suspension. If such action is taken, all effort must be made to ensure the safety of the participants enrolled in the study. The investigator(s) will inform the responsible IECs and provide the reason for the suspension or termination.

In case of premature study or study site closure, the monitor will conduct all activities as indicated above.

12.5 AUDITS AND INSPECTIONS

For the purpose of compliance with ICH-GCP and regulatory guidelines, it may be possible that the sponsor/designee or a national regulatory authority may conduct a site audit/inspection. This may occur at any time from start to after conclusion of the study.

The investigator agrees to allow the auditor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

If a regulatory authority requests an inspection, the investigator must inform the sponsor or its designee immediately about this request. The investigator(s) and the study coordinator(s) must make the relevant records available for inspection and must be available to respond to

reasonable requests and audit queries made by authorized representatives of regulatory agencies. The sponsor will provide any needed assistance in responding to regulatory audits or correspondence.

13. REGULATORY AND ETHICAL REQUIREMENTS

13.1 ETHICS COMMITTEE REVIEW AND COMMUNICATION

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by the IECs responsible for the study sites. The IECs must also review and approve the Informed Consent Form and any other written information to be provided to the participant. Written IEC approval shall be obtained prior to study start.

No deviations from, or changes to, the protocol shall be initiated without prior written IEC approvals of an appropriate amendment, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor(s), telephone number(s)). The investigator shall provide to the sponsors a statement from the IEC confirming the IEC is organized and operates according to GCP and applicable laws and regulations.

13.2 PROTOCOL AMENDMENTS

Any significant change in the study protocol shall be addressed in a written protocol amendment, which will be signed by the investigator(s) and the sponsors. It is the investigator's responsibility to submit protocol amendments to the IECs and to obtain written approval where required.

In some cases, protocol amendments may also be submitted to DCGI.

A protocol amendment may be implemented after it has been approved by IECs. In the case of a protocol change intended to eliminate an apparent immediate hazard to participants, the change may be implemented immediately. In this case, the change must be later documented in an amendment and reported to the IECs as soon as possible. Amendments affecting only logistical or administrative aspects of the study may not require formal IEC approval. Logistical and administrative amendments (e.g., concerning a change of telephone number) shall be submitted to the IECs for information purposes. However, the investigator must

provide the sponsors with written verification that such logistical or administrative amendments are submitted to the relevant IECs.

13.3 PARTICIPANT INFORMATION AND INFORMED CONSENT

Prior to including any participant in the clinical study, his/her free and expressed informed consent must be obtained in writing. Consent must be given with free will of choice, and without inducement.

The investigator or his/her designee shall provide to each potential participant sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision. The investigator shall give the participants ample time and opportunity to inquire about details of the study and ask any questions.

The process for obtaining the informed consent of the participant shall be in accordance with the recommendations in the New Drugs and Clinical Trials Rules, 2019.

The written informed consent must be signed and dated by both investigator/designee and participant prior to any study related procedure. In case of illiterate individuals, the study will be explained to them by the investigator or his/her designee and the Informed consent form (ICF) read for them in the presence of an impartial witness. The witness shall personally sign and date the consent form while a fingerprint will be requested from illiterate individuals. The process of informed consent should be described in source template.

Original ICF must be kept on file by the investigator for possible inspection by IECs member, regulatory authorities and the sponsors (or their designees). Participant must receive a copy of the signed ICF, and any subsequent updates or amendments.

The study monitor shall check the documentation of the individual ICF during each monitoring visit.

13.4 PARTICIPANT CONFIDENTIALITY

The investigator(s) must ensure that participant confidentiality is maintained. Personal identifiers will not be included in any study reports. Participants will be identified by the screening number and by participant initials. If a participant’s name appears on any other

document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor/designee. Study findings stored on a computer will subject to local data protection laws. Participant will be informed that representatives of the sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in the strictest confidence.

13.5 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with:

1. The approved clinical trial protocol,
2. ICH-GCP guidelines.
3. Current revision of the Declaration of Helsinki (Revised Fortaleza, 2013).
4. ICH Harmonized Tripartite Guideline for Good Clinical Practice (E6) 1996.
5. 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines' issued by Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India in 2005.
6. New Drugs and Clinical Trials Rules, 2019 and any amendment thereof
7. 'Ethical Guidelines for Biomedical Research on Human Subjects' issued by Indian Council of Medical Research, 2017.

14. DATA HANDLING AND RECORD KEEPING

In accordance with applicable regulatory requirements, following closure of the study, the investigator/site/institution will maintain a copy of all essential documents in a secure and designated location at the study site. Essential documents shall be retained for at least 5 years after the completion or discontinuation of the study. Sponsor will notify the investigator/institution when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. Signed protocol and all amendments;
2. Ethics committee approval for the study protocol and all amendments;
3. All source documents;
4. eCRF records;

5. Study Participant Informed Consent and
6. Any other pertinent study document.

The document should not be destroyed without the written permission from SIIPL. It is responsibility of SIIPL to inform the study Investigator when these documents no longer need to be retained.

15. INSURANCE AND COMPENSATION OF STUDY PARTICIPANTS

All the study participants in this study are insured by Sponsor against any injury caused by any AE causally related to the study investigational product.

The cost of medical care needed for treatment of vaccine related AEs (including SAEs) occurring among trial participants will be borne by sponsor and as required by the Rules and Regulations passed by DCGI. In case DCGI directs to pay compensation for any AE, sponsor will pay the same and the details of compensation provided would be intimated to the office of the DCGI.

Pending respective site's IEC approval, participants will be compensated for their time in this study, and reimbursed for travel to study visits. The study ICF will state the plan for reimbursement. Study participants will not be charged for study vaccinations, research clinic visits, research-related examinations, or research-related laboratory tests.

PI and delegated study staff as well as IEC members will be insured by Sponsor for this study as per regulatory and ethical requirements.

16. PUBLICATION POLICY & CONFIDENTIALITY

SIIPL and ICMR hold the exclusive rights to publish the study results jointly. Due credit will be given to the investigators in case the results of the study are published.

All proprietary or confidential information communicated to the investigator by or for SIIPL or communicated to the investigator during the course of and/or as a result of the clinical study is the exclusive property of SIIPL, and the investigator shall ensure that the same shall be kept strictly confidential by him/her and any other person connected with the clinical study and shall not be disclosed, either orally or in written form, by him/her or such person to any third party without the prior written consent of SIIPL.

The investigator shall communicate the results of the clinical study promptly to SIIPL.

All rights and interests worldwide in any inventions, know-how, or other intellectual or industrial property rights which arise during the course of and/or as a result of the clinical study which is the subject of this protocol or which otherwise arise from the information or materials supplied under this protocol, shall be assigned to, vest in and remain the property of SIIPL.

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APPENDIX I

SPONSOR'S SIGNATURE PAGE

APPENDIX II

DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX III

INVESTIGATOR'S STATEMENT OF COMPLIANCE

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the approved clinical trial protocol, institution ethics committee and informed consent regulations and ICH GCP guidelines. The study will be conducted according to current revision of the Declaration of Helsinki (Revised Fortaleza, 2013). In addition, most current version of local regulatory and ethical requirements 'Guidelines for Clinical Trials on Pharmaceutical Products in India – GCP Guidelines' issued by Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India in 2005, 'Requirements and guidelines for permission to import and / or manufacture of new drugs for sale or to undertake clinical trials' (New Drugs and Clinical Trials Rules, 2019) and it's amended rules and 'Ethical Guidelines for Biomedical Research on Human Subjects' issued by Indian Council of Medical Research will be adhered to.

Principal Investigator	Signature	Date

APPENDIX IV

STUDY SITES AND PRINCIPAL INVESTIGATOR INFORMATION

GENRAL INFORMATION: PRINCIPAL INVESTIGATORS AND STUDY SITES

Title:	A PHASE 2/3, OBSERVER-BLIND, RANDOMIZED, CONTROLLED STUDY TO DETERMINE THE SAFETY AND IMMUNOGENICITY OF COVISHIELD (COVID-19 VACCINE) IN HEALTHY INDIAN ADULTS
Protocol No. **Version and Date**	ICMR/SII-COVISHILED Version: 5.0 Dated 06 Feb 2021
Phase:	2/3
Sponsor	**SERUM INSTITUTE OF INDIA PVT. LTD.** 212/2, Hadapsar, Pune-411028 [redacted] **INDIAN COUNCIL OF MEDICAL RESEARCH** V. Ramalingaswami Bhawan, P.O. Box No. 4911 Ansari Nagar, New Delhi - 110029, India
Principal Investigators and study sites	[redacted]

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APPENDIX V

DIVISION OF AIDS (DAIDS) TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS, CORRECTED VERSION 2.1, JULY 2017

Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events

Corrected Version 2.1
July 2017

Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
US Department of Health and Human Services

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Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (*serum glutamic pyruvic transaminase)*
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (*serum glutamic-oxaloacetic transaminase)*
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: <u>Adults</u> Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. <u>Young Children</u> Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Introduction

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS grading table.

Instructions for Use

General Considerations

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use age and sex values as applicable.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

Instructions for Use

When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies- *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – *http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables*

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1]				
Hypertension *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Systemic

Serum Sickness[10]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

*Laboratory Values**
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*)				
≥ *7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 ≥ *3.38*
< *7 days of age*	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*)				
≥ *7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< *7 days of age*	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*)				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 ≥ *27.75*

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glucose, Low (mg/dL; *mmol/L*)				
≥ 1 month of age	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], High (mg/dL; *µmol/L*)[19]				
Term Neonate[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171* to < *290.7*	≥ 17 ≥ *290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2* to < *324.9*	≥ 19 ≥ *324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5* to < *376.2*	≥ 22 ≥ *376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8* to < *410.4*	≥ 24 ≥ *410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 ≥ *239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 ≥ *136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 ≥ *427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.