Protocol Numbers: 81803 (V9), 81800 (V4), BCOV22 (V3)	**Statistical Analysis Plan**

JOINT STATISTICAL ANALYSIS PLAN FOR:

PROTOCOL 81803: A randomised controlled trial to assess the immunogenicity, safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccines (Pfizer-BioNTech, Moderna, or AstraZeneca) given as a booster dose after priming with CoronaVac or AstraZeneca in healthy adults in Indonesia

PROTOCOL 81800: A randomised controlled trial to assess the immunogenicity, safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccines (Pfizer-BioNTech) given as an additional dose after priming with Sinopharm, AstraZeneca, or Sputnik in healthy adults in Mongolia

PROTOCOL BCOV22: An observational study, following a trial, to assess the immunogenicity and safety of standard dose versus fractional doses of COVID-19 vaccines (Pfizer-BioNTech or AstraZeneca) or standard dose Coronavac given as an additional dose after priming with Coronavac or AstraZeneca in health adults in Indonesia

Trial Registrations: NCT05265065 and NCT05387317

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This document has been written based on information contained in study protocols 81803 (Version 9.0, 18th August 2022), 81800 (Version 4.0, 2nd May 2022), and BCOV22 (Version 3.0, 27th April 2022).

Version 2.0

Protocol Numbers: 81803 (V9), 81800 (V4), BCOV22 (V3)	Statistical Analysis Plan

Document Version History

Protocol Versions	SAP Version	Date	Contributor	Change Description	Reason/ Comment	Contributor Signature & Date	Senior Statistician Signature & Date	Sponsor-Investigator Signature & Date	Principal Investigator Signature & Date
81803 (V9) 81800 (V4) BCOV22 (V3)	1.0	4-Oct-2022	Kerryn Moore	Initial release.	Not applicable.	Kerryn Moore KERRYN MOORE			
81803 (V9) 81800 (V4) BCOV22 (V3)	2.0	23-May-2024	Kerryn Moore	Did not include Mongolia-specific identifier (NCT05265065). Date 4/10/2022 on page 2 was ambiguous.	clinicaltrials.gov requested changes	Kerryn Moore KERRYN MOORE			

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LIST OF ABBREVIATIONS

AE	Adverse Event
ACE2	Angiotensin converting enzyme-2
CEPI	Coalition for Epidemic Preparedness Innovations
CMI	Cell-mediated immunity
CMIA	Chemiluminescent microparticle immunoassay
ELISA	Enzyme-Linked Immunosorbent Assay
GM	Geometric Mean
GMR	Geometric Mean Ratio
PBMC	Peripheral blood mononuclear cells
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
MCRI	Murdoch Children's Research Institute
RBD	Receptor Binding Domain
RCH	Royal Children's Hospital

1 PROTOCOLS COVERED BY THIS STATISTICAL ANALYSIS PLAN

This statistical analysis plan has been written for three separate protocols for country-specific studies with near-identical study designs in Indonesia and Mongolia:

1. Protocol 81803, Indonesia – the "Indonesia Trial", registered as NCT05387317
2. Protocol 81800, Mongolia – the "Mongolia Trial", registered as NCT05265065)
3. Protocol BCOV22, Indonesia – the "Indonesia Observational Study" or "BCOV22"

BCOV22 is an observational study to provide extended follow-up to 12-months for a recently completed 28-day long trial ("BCOV21"). BCOV21 will provide the baseline and Day-28 data for the BCOV22 analysis.

1.1 GENERIC TERMINOLOGY

The country-specific studies differ primarily in the trial vaccines being studied and the primary series strata, determined by which booster vaccines are available and which priming vaccines were most used in each country. For text that is relevant to all countries, generic terminology will be used:

- "Trial vaccines" refers to:
  - Indonesia Trial: Pfizer (Comirnaty®), Moderna (Spikevax®), or AstraZeneca (Vaxzevria®)
  - BCOV22 (and BCOV21): Pfizer (Comirnaty®) or AstraZeneca (Vaxzevria®)
  - Mongolia Trial: Pfizer (Comirnaty®) only
- "Included primary series" refers to:
  - Indonesia Trial and BCOV22 (and BCOV21): Two doses of either Sinovac (CoronaVac®) or AstraZeneca (Vaxzevria®)
  - Mongolia Trial: Two doses of either Sinopharm (Covilo®), AstraZeneca (Vaxzevria®), or Gamaleya (Sputnik®) vaccines

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary immunogenicity objectives for each study (as worded in the protocols) are to:

- **INDONESIA TRIAL:** Assess and compare the immune response measured as binding antibodies (IgG CMIA) following standard versus fractional doses of Pfizer, Moderna, or AstraZeneca vaccine given as a single booster dose to adults 18 years or older in Indonesia who have been primed through previous vaccination with CoronaVac or AstraZeneca vaccines. (Timepoint – 28 days post-vaccination)

- **MONGOLIA TRIAL:** Assess and compare the immune response measured as binding antibodies (IgG ELISA) following standard versus fractional doses of Pfizer vaccine given as a single additional dose to adults 18 years or older in Mongolia who have been primed through previous vaccination with Sinopharm, AstraZeneca, or Sputnik vaccines. (Timepoint – 28 days post-vaccination)
- **BCOV22:** Assess and compare the immune response over 12 months, measured as binding antibodies (IgG CMIA) following fractional versus standard doses of Pfizer or AstraZeneca or standard dose CoronaVac, given as a single additional dose in adults aged 18 years or more in Indonesia primed through previous vaccination with AstraZeneca or CoronaVac vaccines. (Timepoint not specified in protocol)

The primary safety objective for the Indonesia and Mongolia trials (as worded in the protocols) is to:

- Assess the rate and severity of reactogenicity within one-week post-booster for each group. (Timepoint – daily, for seven days post vaccination)

(There is no primary safety objective for the BCOV22 study, as safety was assessed in the BCOV21 trial.)

2.2 ESTIMANDS

The Estimands (for each trial vaccine) for the primary immunogenicity objective (for the trials) are:

- **INDONESIA Trial:** the difference in seroresponse proportions 28 days after boosting with a single fractional dose compared to a single standard dose of either of the COVID-19 trial vaccines (Comirnaty®, Spikevax®, or Vaxzevria®) in adults 18 years or older in Indonesia who have been primed through previous vaccination with CoronaVac® or Vaxzevria® vaccines, irrespective of SARS-CoV-2 infection.

- **MONGOLIA Trial:** the difference in seroresponse proportions 28 days after boosting with a single fractional dose compared to a single standard dose of the COVID-19 trial vaccine Comirnaty®, in adults 18 years or older in Mongolia who have been primed through previous vaccination with Covilo®, Vaxzevria®, or Sputnik® vaccines, irrespective of SARS-CoV-2 infection.

(As BCOV22 is only providing extended follow-up for the completed and analysed BCOV21 trial, all Estimands for BCOV22 correspond to the 6- and 12-month secondary endpoints in the Indonesia and Mongolia trials, which are specified in section 5.2 Secondary endpoints and 6.14 Analysis of secondary endpoints; in addition the 28-Day endpoint for ACE2 binding inhibition will be analysed under BCOV22 on complete data [ACE2 binding inhibition was measured for only a subset of participants in BCOV21; BCOV22 will complete measurements for all participants using samples collected in BCOV21].)

2.3 FRAMEWORK

The null hypothesis (H_0) is that, following priming through prior vaccination with one of the included primary series, a fractional dose of either of the COVID-19 trial vaccines is inferior to the standard dose of the same vaccine, with a difference in the day-28 seroresponse rate of more than -10% (calculated as the percentage of participants who serorespond in the fractional dose group minus that in the standard dose group). The alternative

hypothesis (H_1) is that a fractional dose is non-inferior to the standard dose, with a difference in the day-28 seroresponse rate of less than -10%. Evidence for or against the null hypothesis will be determined from a two-sided 95% confidence interval rather than a p-value. If the lower confidence limit is above -10% H_0 [inferiority] will be rejected, and the fractional dose will be considered non-inferior. If the confidence interval overlaps -10%, the trial will be inconclusive. If the upper confidence limit is below -10% H_0 [inferiority] will be accepted. The comparison between fractional and standard dose groups will be done separately for each trial vaccine.

2.4 SECONDARY OBJECTIVES

Secondary objectives common to all studies (as worded in the protocols) are to:

- Compare the immunogenicity, both humoral and cellular, over 12 months following fractional and standard booster doses of the vaccines listed.
    - [or equivalently in BCOV22: Compare the magnitude and duration of humoral immunity over 12 months across the different booster vaccine groups.]
- Evaluate the different priming capacities of the different included primary series.
- Evaluate the safety of the booster dose regimens.
    - [or equivalently in Indonesia Trial: Evaluate the longer-term safety and reactogenicity of the booster regimens].

Additional secondary objectives in the Indonesia Trial and BCOV22 (as worded in the protocol) are to:

- Identify any difference in the risk of clinically significant COVID-19 cases between any of the study groups.

An additional secondary objective in the Mongolia Trial (as worded in the protocol) is to:

- Assess the impact of prior natural exposure on boosting regimens.

3 BACKGROUND AND INTRODUCTION

3.1 STUDY DESIGN: INDONESIA TRIAL

The Indonesia Trial is a single-blind six-arm randomised controlled non-inferiority trial (1:1:1:1:2:2) looking at the immunogenicity, safety, and reactogenicity over 12 months of fractional vs. standard doses of COVID-19 vaccines (Pfizer-BioNTech [*Comirnaty®*], Moderna [*Spikevax®*], and AstraZeneca [*Vaxzevria®*]) in healthy adults aged 18 years or older in Indonesia who have received two primary doses of either Sinovac [*CoronaVac®*] or AstraZeneca [*Vaxzevria®*] vaccines 6 months prior to enrolment.

The trial will be conducted at Indonesia's Faculty of Medicine Universitas Padjadjaran, with three study sites: Puskesmas (Clinic) Garuda, Puskesmas (Clinic) Ciumbuleuit and Puskesmas (Clinic) Dago in Bandung, West Java, Indonesia. 800 participants will be randomised 1:1:1:1:2:2 to fractional or

standard doses of *Comirnaty®*, *Vaxzevria®*, or *Spikevax®*, with stratification by the primary vaccine received (*CoronaVac®* or *Vaxzevria®*) and age (<50 and ≥50 years) to ensure balance between the arms with respect to these key factors. Target recruitment quotas will be set with the aim of recruiting equal numbers into each of the primary series (400:400) and age (400:400) strata. Additionally, 80 participants from each study group (480 total, with 1:1:1:1:1:1 randomisation) will be included in a sub-study of cell-mediated immunity (CMI).

Participants will be followed for 12 months. Immunogenicity outcomes (humoral and cellular immunity) will be measured at baseline, 28 days, 6 months, and 12 months. Safety and reactogenicity outcomes will be collected from baseline to 7 days (solicited AE), 28 days (unsolicited AE), 3 months (medically attended AE), and 12 months (SAE).

The protocol specifies that if fractional dose responses are considered inadequate (undefined) an appropriate rescue strategy will be developed, probably involving a single dose (dosage not specified) of the vaccine in question at 3 months.

3.2 STUDY DESIGN: INDONESIA (BCOV21 AND BCOV22)

The BCOV21 Trial was a single-blind five-arm randomised controlled non-inferiority trial sponsored by the Indonesian Government looking at the immunogenicity, safety, and reactogenicity over 3 months of fractional vs. standard doses of COVID-19 vaccines (Pfizer-BioNTech [*Comirnaty®*] and AstraZeneca [*Vaxzevria®*]) in healthy adults aged 18 years or older in Indonesia who have received two primary doses of either *CoronaVac®* 3-5 months prior to enrolment, *CoronaVac®* 6-9 months prior to enrolment, or *Vaxzevria®* 6-9 months prior to enrolment.

The trial was conducted at Bandung and Jakarta, Indonesia. 1000 participants who had been primed with *CoronaVac®* (3-5 months or 6-9 months prior to enrolment) were randomised 1:1:1:1:1 to fractional or standard doses of *Comirnaty®* or *Vaxzevria®*, or a standard dose of *CoronaVac®*, with stratification by the primary vaccine received (*CoronaVac®* 3-5 months prior or *CoronaVac®* 6-9 months prior) and age (<60 and ≥60 years) to ensure balance between the arms with respect to these key factors. Additionally, 400 participants who had been primed with *Vaxzevria®* 6-9 months prior to enrolment were randomised 1:1:1:1 to fractional or standard doses of *Comirnaty®* or *Vaxzevria®*, with stratification by age (<60 and ≥60 years) to ensure balance between the arms with respect to age. Recruitment within each stratum was stopped once quotas were reached to ensure that the number of participants in each of the primary series strata were equal and that 20% of participants were ≥60 years of age (recruitment into the older age stratum fell slightly short of the quotas).

Participants were followed for 28 days. Recruitment and follow up for BCOV21 had finished at the time of writing the SAP. Immunogenicity outcomes (humoral immunity only) were measured at baseline and 28 days. Safety and reactogenicity outcomes were collected from baseline to 7 days (solicited AE), 28 days (unsolicited AE).

Rescue vaccination was offered to participants who received *CoronaVac®* based on Day-28 outcomes, which was taken up by most participants in the *CoronaVac®* arm; the rescue vaccination was provided under the public health system.

The BCOV22 Observational Study (sponsored by MCRI) has invited all participants of BCOV21 for extended follow-up to 12 months, with immunogenicity outcomes measured at Month-6 and Month-12 (timepoints from the start of BCOV21). Day-28 BCOV21 samples not previously analysed for some immunogenicity outcomes will be tested as part of BCOV22.

3.3 STUDY DESIGN: MONGOLIA TRIAL

The Mongolia Trial is a single-blind two-arm randomised controlled non-inferiority trial (1:1) looking at the immunogenicity, safety, and reactogenicity over 12 months of fractional vs. standard doses of the COVID-19 vaccine Pfizer-BioNTech [*Comirnaty*] in healthy adults aged 18 years or older in Mongolia who have received two primary doses of either Sinopharm [*Covilo*®], AstraZeneca [*Vaxzevria*®], Gamaleya [*Sputnik*®] vaccines 6 months prior to enrolment.

The trial will be conducted at multiple sites (vaccination clinics) in Ulaanbaatar. Participants will be randomised 1:1 to fractional or standard doses of *Comirnaty*®, with 400 participants per arm, and stratification by the primary vaccine received (*Covilo*®, *Vaxzevria*®, or *Sputnik*®) (target recruitment quotas 200:100:100) and age (<50 and ≥50 years) (target recruitment quotas 200:200) to ensure balance between the arms with respect to these key factors. Additionally, 40% of participants from each study group will be included in a sub-study of cell-mediated immunity (CMI).

Participants will be followed for 12 months. Immunogenicity outcomes (humoral and cellular immunity) will be measured at baseline, 28 days, 6 months, and 12 months. Safety and reactogenicity outcomes will be collected from baseline to 7 days (solicited AE), 28 days (unsolicited AE), 3 months (medically attended AE), and 12 months (SAE).

The protocol specifies that if fractional dose responses are considered inadequate (undefined) an appropriate rescue strategy will be developed, probably involving a single dose (dosage not specified) of the vaccine in question at 3 months.

3.4 STUDY GROUPS AND RANDOMISATION

Table 1 provides a brief description of the trial vaccines. Further information on the trial vaccines, including active substances, mode of action, dosage, and administration are provided in the Protocols. Dose modifications are not permitted and must be given as per randomisation.

Table 1. Summary of trial vaccines

Country	Study Group	Generic vaccine name	Route	Dose
Indonesia Trial	*Comirnaty*® standard full dose	Pfizer-BioNTech (BNT162b2)	IM	30µg
	Comirnaty® fractional dose	Pfizer-BioNTech	IM	15µg

		(BNT162b2)		
	Spikevax® standard full dose	Moderna (mRNA-1273)	IM	50µg
	Spikevax® fractional dose	Moderna (mRNA-1273)	IM	20µg
	Vaxzevria® standard full dose	AstraZeneca (ChAdOx1-S)	IM	5 x 10^{10}vp in 0.5ml
	Vaxzevria® fractional dose	AstraZeneca (ChAdOx1-S)	IM	2.5 x 10^{10}vp in 0.25ml
Indonesia BCOV21/22	*Comirnaty*® standard full dose	Pfizer-BioNTech (BNT162b2)	IM	30µg
	Comirnaty® fractional dose	Pfizer-BioNTech (BNT162b2)	IM	15µg
	Vaxzevria® standard full dose	AstraZeneca (ChAdOx1-S)	IM	5 x 10^{10}vp in 0.5ml
	Vaxzevria® fractional dose	AstraZeneca (ChAdOx1-S)	IM	2.5 x 10^{10}vp in 0.25ml
	CoronaVac® standard dose	Sinovac	IM	3µg or 600 SU in 0.5ml
Mongolia Trial	*Comirnaty*® standard full dose	Pfizer-BioNTech (BNT162b2)	IM	30µg
	Comirnaty® fractional dose	Pfizer-BioNTech (BNT162b2)	IM	15µg

IM: Intramuscular. Colours are used to highlight common study groups across countries.

Participants will be randomised into one of the trial vaccine study groups, with stratification by the primary series, age (<50 and ≥50 years) and CMI study group (included in CMI sub-study, or main study only), as described in 3.1 (Indonesia), and 3.3 (Mongolia), and (Table 2). A secure, password-protected web-based randomisation schedule will be provided by an independent statistician from the Melbourne Children's Trial Centre at the MCRI. Blocked randomisation will be used with random blocks of permuted length. To ensure pre-specified target numbers by primary series and age group strata, participants will be recruited until the number required in each stratum has been reached. 40% of participants from each group in Mongolia will be included in the cell mediated immunity (CMI) subgroup analysis (360 and 180 total, respectively); in Indonesia, 80 participants from each arm will be included in the CMI subgroup analysis (480 total). Measures will be taken to ensure that the age strata (<50 and ≥50 years) are equally represented in the CMI sub-study group. Only 10-20 CMI samples can be processed per day. The site teams will therefore recruit the first 10-20 participants who consent to participate in this sub-study per day. Daily recruitment will be stopped once each subset is complete. Details of the randomisation method are held securely in a REDCap database by the Clinical Epidemiology and Biostatistics Unit (CEBU) at MCRI.

Table 2. Study groups and strata

	Trial arms			Stratification*		
Country	**Study group**	**N**	**Intervention/Comparison**	**Primary series**	**Age Group**	**N**
Indonesia Trial	*Comirnaty*® standard full dose	100#	Comparison (to *Comirnaty*®)	*Vaxzevria*®	<50 years	25

(1:1:1:1:2:2)			fractional dose)	*Vaxzevria*®	≥50 years	25
				CoronaVac®	<50 years	25
				CoronaVac®	≥50 years	25
	Comirnaty® fractional dose	100#	Intervention - *Comirnaty*®	*Vaxzevria*®	<50 years	25
				Vaxzevria®	≥50 years	25
				CoronaVac®	<50 years	25
				CoronaVac®	≥50 years	25
	Vaxzevria® standard full dose	100#	Comparison (to *Vaxzevria*® fractional dose)	*Vaxzevria*®	<50 years	25
				Vaxzevria®	≥50 years	25
				CoronaVac®	<50 years	25
				CoronaVac®	≥50 years	25
	Vaxzevria® fractional dose	100#	Intervention - *Vaxzevria*®	*Vaxzevria*®	<50 years	25
				Vaxzevria®	≥50 years	25
				CoronaVac®	<50 years	25
				CoronaVac®	≥50 years	25
	Spikevax® standard full dose	200	Comparison (to *Spikevax*® fractional dose)	*Vaxzevria*®	<50 years	50
				Vaxzevria®	≥50 years	50
				CoronaVac®	<50 years	50
				CoronaVac®	≥50 years	50
	Spikevax® fractional dose	200	Intervention - *Spikevax*®	*Vaxzevria*®	<50 years	50
				Vaxzevria®	≥50 years	50
				CoronaVac®	<50 years	50
				CoronaVac®	≥50 years	50
Indonesia BCOV21/22	*Comirnaty*® standard full dose	300^	Comparison (to *Comirnaty*® fractional dose)	*Vaxzevria*®	<60 years	50
				Vaxzevria®	≥60 years	50
				CoronaVac® 3-5m	<60 years	50
				CoronaVac® 3-5m	≥60 years	50
				CoronaVac® 6-9m	<60 years	50
				CoronaVac® 6-9m	≥60 years	50
	Comirnaty® fractional dose	300^	Intervention - *Comirnaty*®	*Vaxzevria*®	<60 years	50
				Vaxzevria®	≥60 years	50
				CoronaVac® 3-5m	<60 years	50
				CoronaVac® 3-5m	≥60 years	50
				CoronaVac® 6-9m	<60 years	50
				CoronaVac® 6-9m	≥60 years	50
	Vaxzevria® standard full dose	300^	Comparison (to *Vaxzevria*® fractional dose)	*Vaxzevria*®	<60 years	50
				Vaxzevria®	≥60 years	50
				CoronaVac® 3-5m	<60 years	50
				CoronaVac® 3-5m	≥60 years	50
				CoronaVac® 6-9m	<60 years	50

				CoronaVac® 6-9m	≥60 years	50
	Vaxzevria® fractional dose	300^	Intervention - *Vaxzevria®*	*Vaxzevria®*	<60 years	50
				Vaxzevria®	≥60 years	50
				CoronaVac® 3-5m	<60 years	50
				CoronaVac® 3-5m	≥60 years	50
				CoronaVac® 6-9m	<60 years	50
				CoronaVac® 6-9m	≥60 years	50
	CoronaVac® standard dose	200^	*NA*	CoronaVac® 3-5m	<60 years	50
				CoronaVac® 3-5m	≥60 years	50
				CoronaVac® 6-9m	<60 years	50
				CoronaVac® 6-9m	≥60 years	50
Mongolia Trial (1:1)	*Comirnaty®* standard full dose	400	Comparison (to *Comirnaty®* fractional dose)	Covilo®	<50 years	100
				Covilo®	≥50 years	100
				Vaxzevria®	<50 years	50
				Vaxzevria®	≥50 years	50
				Sputnik®	<50 years	50
				Sputnik®	≥50 years	50
	Comirnaty® fractional dose	400	Intervention - *Comirnaty®*	Covilo®	<50 years	100
				Covilo®	≥50 years	100
				Vaxzevria®	<50 years	50
				Vaxzevria®	≥50 years	50
				Sputnik®	<50 years	50
				Sputnik®	≥50 years	50

*In addition to the primary series and age strata, participants will be stratified for inclusion into a CMI sub-study: 80 participants from each arm in Indonesia (total 480); 40% of participants from each stratum in Mongolia (total 160). #These groups will be supplemented with concatenated data from BCOV21/22 (up to 300 participants per study group) in a combined analysis. 3-5m and 6-9m refers to the months prior to enrolment that the primary series was received. ^Numbers are for recruitment into BCOV21; numbers in BCOV22 will depend on recruitment rates into BCOV22. Further, BCOV21 recruitment has finished and fell short of recruitment targets in the CoronaVac primed ≥60 years group by 40 participants across all arms.

3.5 BLINDING

Study staff involved in administering the vaccine will be unblinded. The participants and study staff involved in assessing reactogenicity will be blinded to their group allocation until the Day-28 visit. Study staff involved in assessing immunogenicity outcomes will remain blinded during the analysis of specimens. In the unlikely event that it becomes necessary to unblind prior to the Day-28 visit that decision will be taken by the PI, and the participant and physicians who may be caring for the participant will be made aware of the allocation. Statisticians and analysts will remain blinded during the development of the SAP (approved by the Trial Steering Committee). Further, statisticians and analysts will develop and finalise all codes using a dummy variable for treatment allocation. If SAP revisions related to comparative analyses are required after codes have been run using the real allocations, the staff involved in deciding, writing, and approving these revisions will not have access to the data with the real allocations.

3.6 STUDY POPULATION: ELIGIBILITY AND SCREENING

The study populations and Pre-Screening methods for each country are detailed in the sections below.

In all countries, participants are consented at the Day-0 visit (after Pre-Screening), and a post-consent assessment is conducted to determine final eligibility. Those who provide consent but are determined to be ineligible are termed screen failures. The number of screen failures will be reported with reasons.

3.6.1 Indonesia Trial

Trial participants will be healthy adults aged 18 years or older in Indonesia who have received two primary doses of either Sinovac [*CoronaVac®*] or AstraZeneca [*Vaxzevria®*] 6 months prior to enrolment. Participants will be recruited from three clinics (Garuda, Ciumbuleuit, and Dago) in Bandung, West Java, Indonesia. Inclusion and exclusion criteria are listed in the Protocol.

At each recruiting clinic, records of COVID-19 immunization will be reviewed to identify potential participants (adults who have received two priming doses of *Vaxzevria®* or *CoronaVac®* over 6 months ago and have not yet received a third dose) (Pre-Screening). Potential participants will be contacted by the clinic personnel to give initial information about the study and invite the potential participant to attend an in-person screening visit. A record of all potential participants from Pre-Screening who attend the in-person screening visit will be recorded in a recruitment log. If the potential participant decides not to participate no identifying information will be retained.

3.6.2 Indonesia BCOV22 Observational Study

Trial participants will be healthy adults aged 18 years or older in Indonesia who have received two primary doses of either Sinovac [*CoronaVac®*] or AstraZeneca [*Vaxzevria®*], and who were enrolled into BCOV21. BCOV21 recruited participants from Bandung and Jakarta, Indonesia. All BCOV21 participants will be approached for recruitment into BCOV22. Inclusion and exclusion criteria are listed in the Protocol.

3.6.3 Mongolia Trial

Trial participants will be healthy adults aged 18 years or older in Mongolia who have received two primary doses of either Sinopharm [*Covilo®*], AstraZeneca [*Vaxzevria®*], or Gamaleya [*Sputnik®*] 6 months prior to enrolment. Participants will be recruited at multiple sites (vaccination clinics) in Ulaanbaatar. Inclusion and exclusion criteria are listed in the Protocol.

The study will be offered to people attending participating clinics for their third dose (Pre-Screening). Those interested will be provided with the participant information sheet and consent form and a member of the research team will be available to answer their questions. If recruitment is slow, the study may be promoted by the Ministry of Health through their daily media briefings. A record of all potential participants from Pre-Screening will be recorded on a recruitment log. If the potential participant decides not to participate no identifying information will be retained.

3.7 SAMPLE SIZE

Details of sample size calculations are provided in the protocols.

3.8 STUDY PROCEDURE

Figure 1 provides a summary of the study procedures. A participant will be considered lost to follow-up if they fail to return for two consecutive visits and cannot be contacted by the trial staff.

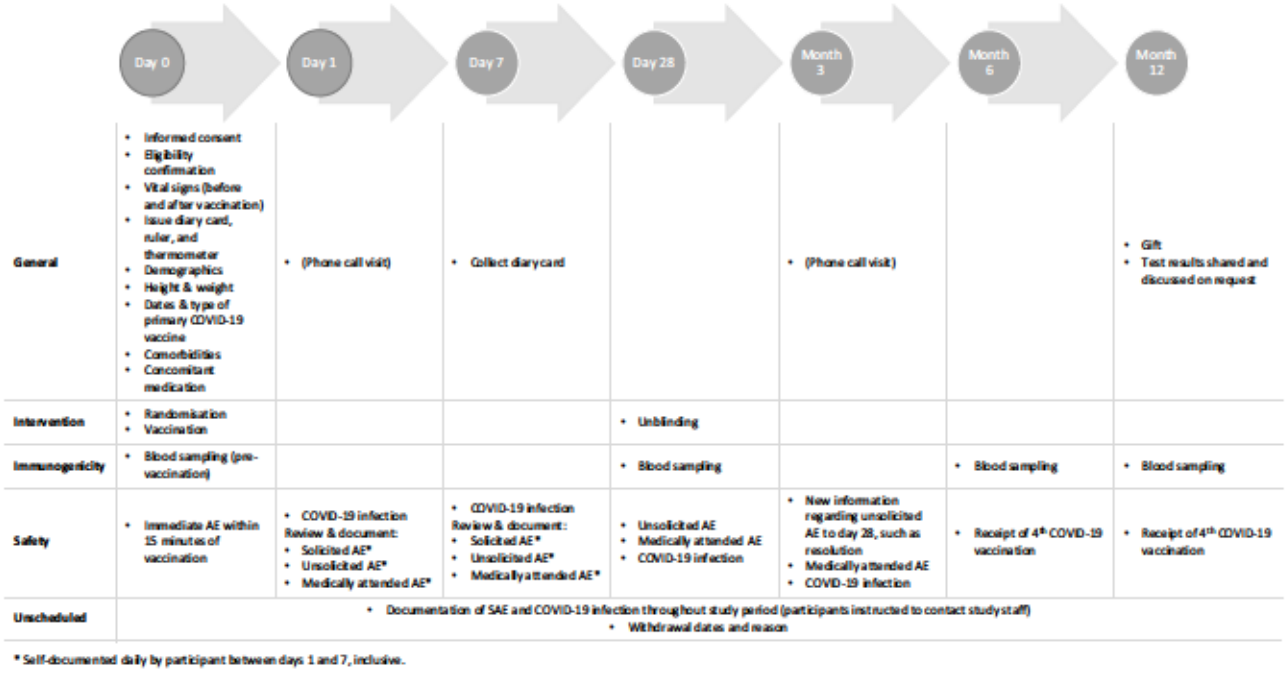


Figure 1. Timeline of trial procedures. BCOV22 begins at the Month 6 visit; data will be concatenated with BCOV21, providing data for all visits prior to Month 6 (Day 0 – Day 28).

4 OUTCOME VARIABLES AND OTHER PARAMETERS

4.1 IMMUNOGENICITY OUTCOMES

Table 3 describes the immunogenicity outcome variables.

Table 3. Description of outcome variables

	Outcome	Subset	Units	Timepoints^
Humoral immunity	Seroresponse (see 5.1.1 for definition)	All	Binary (yes/no)	Day 28

(antibodies)	Binding antibody (IgG)	*ACE2 binding inhibition was measured for only a subset of participants in BCOV21 (Day-28) – BCOV22 will complete measurements for all participants using samples collected in BCOV21.*	BAU/ml[#]	Day 28 Month 6 Month 12
	ACE2 binding* inhibition by neutralising antibody (wild type)		% Binding inhibition	Day 28 Month 6 Month 12
	ACE2 binding* inhibition by neutralising antibody (Omicron)			
	Neutralising antibody (wild type)	MCRI-Mongolia Trial: 20% in Mongolia Indonesia Trial: 40 participants in the *Spikevax®* arms (10 per primary vaccine strata for each dose allocation group) BCOV22: 140 participants (10 per primary vaccine strata for each dose allocation group and trial vaccine)	NT_{50}	Day 28 Month 6 Month 12
	Neutralising antibody (Delta)			
	Neutralising antibody (Omicron)			
Cellular immunity (CMI sub-study)	IFNγ	Indonesia Trial: 80 participants per arm (480 total) Mongolia Trial: 40% per strata (160 total) BCOV22: no CMI analysis (0 total)	IU/ml	Day 28 Month 12
	IFNγ-producing cells		cells/million PBMCs	Day 28 Month 12
	Cytokine-expressing T cells *(multiple outcomes for several cytokines^)*		Frequency (%) of cell subset	Day 28 Month 12

	Cytokine concentration *(multiple outcomes for several cytokines^)*		pg/ml	Day 28 Month 12

*Between the SARS-CoV-2 receptor binding domain and the host-cell ACE2 (angiotensin converting enzyme-2) receptor. #Binding antibody will be measured as relative units/ml (RU/ml) as per the manufacturer's instructions, and converted to binding antibody units (BAU/ml) using the WHO reference serum from NIBSC, UK. ^Specific cytokines are yet to be specified. ^Baseline measurements are also taken at Day 0.

4.2 REACTOGENICITY AND SAFETY OUTCOMES

Table 4 summarises the reactogenicity and safety outcomes and relevant parameters. Further details on all collected parameters are stored in RedCAP Codebooks, as detailed in the Data Management Plan. Definitions of the terms adverse event, adverse reaction, and serious adverse event are given in the Protocols, and are aligned with definitions used in trials involving investigational medicinal products.

Table 4. Reactogenicity and safety outcomes

Outcome	Parameter	Categories	Timepoints
Reactogenicity (local)	Pain	Grade 0, 1, 2, 3, or 4*	Day 1, 2, 3, 4, 5, 6, & 7
	Tenderness		
	Redness		
	Swelling		
	Hardness		
	Axillary lymphadenopathy		
	Warmth	Binary (presence/absence)	
	Itch		
Reactogenicity (general/systemic)	Fever	Grade 0, 1, 2, 3, or 4*	
	Nausea		
	Vomiting		
	Diarrhoea		
	Headache		
	Fatigue/Malaise		
	Myalgia		

	Arthralgia		
Adverse Events to 28 Days Adverse Reaction to 28 Days[δ] Serious Adverse Events to 12 months	Experienced an adverse event	Binary (yes/no)	Adverse Events to 28 Days: Day-0, -1, -7, and -28 visits, and Month-3 visit (for new information, e.g., resolution) Serious Adverse Events to 12 months: Unscheduled (participants instructed to contact study staff)
	System Organ Class^	As per MedDRA	
	Severity	Severity Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (fatal)[#]	
	Outcome	1-Resolved 2-Resolved with sequelae 3-Ongoing 4-Fatal 5-Unknown	
	Serious	Binary (yes/no)	
	Onset (days from trial vaccination)	*Continuous*	
	Event duration (days)	*Continuous*	
	Relatedness	1-Unrelated 2-Possible 3-Probable 4-Definite	

*5-point severity scale: 0-None; 1-Mild; 2-Moderate; 3-Severe; 4-Life-threatening. *Refer to Protocol for more detailed definitions*. Grading for hardness and swelling in Mongolia will not consider interference with daily activities as per the protocol as this information is not being captured. [#]Grade 3-4 events may be SAEs; all Grade 5 events are automatically considered as SAEs. ^Will require derivation from 'event_term' and 'saefin' fields by study team. [δ]An adverse reaction is an adverse event with causality assessment of either Possible, Probable, or Definite.

4.3 DEMOGRAPHY AND BASELINE

At the Day 0 visit, information is collected on the participant's primary series (including vaccine, dates, and any reactions experienced), demographics (age, sex, ethnicity), comorbidities, and clinical observations prior to trial vaccination. Details of demography and baseline parameters are stored in RedCAP Codebooks, as detailed in the Data Management Plan.

4.4 INTERCURRENT EVENTS

Data will be collected throughout the 12-month follow-up period on receipt of a 4th dose (including date and vaccine) and breakthrough SARS-CoV-2 infections (including date and severity). These will be considered as intercurrent events in the analysis; the strategies that will be used for handling these events are detailed in Estimand-to-Analysis tables in 6.13 Analysis of the primary endpoints and 6.14 Analysis of secondary endpoints. Intercurrent event parameters are detailed in Section 4.4 Intercurrent events.

Intercurrent event	Potential impact if ignored
Breakthrough SARS-CoV-2 infection	Breakthrough infections will have a boosting effect on immunological markers, making the trial vaccine appear more immunogenetic than it truly is. High incidence of breakthrough infections due to reduced immunogenicity in one group could give the appearance of greater immunogenicity of the trial vaccination in this group relative to other groups in which breakthrough infections have been more successfully prevented.
Receipt of 4th dose (self-initiated or sponsor-initiated, i.e. rescue)	Receipt of a 4th dose will have a boosting effect on immunological markers, making the trial vaccine appear more immunogenetic than it truly is. Higher uptake of the 4th dose in one group (e.g. due to rescue of fractional dose recipients) could give the appearance of greater immunogenicity of the trial vaccination in this group relative to other groups with lower 4th dose uptake.

Lost-to-follow-up and other events resulting in missing data will be treated as a missing data problem and handled using multiple imputation.

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

5.1.1 Seroresponse at Day-28

The primary endpoint is seroresponse at the Day-28 visit, comparing the fractional dose group to the standard dose group for each booster vaccine. Seroresponse at the individual level is defined as a ≥4-fold rise in binding antibodies at the Day-28 visit compared to baseline (pre-vaccination), or a ≥2-fold rise among participants with a baseline (pre-vaccination) titre of ≥200 BAU/ml (Table 5).

Table 5. Thresholds to define seroresponse in an individual at the Day-28 visit, by baseline binding antibody titre

Baseline binding antibody titre	Threshold for seroresponse at 28 days
Below limit of detection (<100 BAU/ml)	≥ 4 x lower limit of detection (100 BAU/ml) ("4-fold rise"), i.e. ≥ 400 BAU/ml
<200 BAU/ml	≥ 4 x baseline ("4-fold rise")
≥200 BAU/ml	≥ 2 x baseline ("2-fold rise")

5.1.2 Reactogenicity within 7 days of boosting

Reactogenicity will be measured using a standardised daily questionnaire (diary card) that elicits the presence and severity (mild, moderate, severe, life-threatening [grades 1-4, respectively]), or absence, of local reactions (pain, tenderness, redness, hardness, swelling, necrosis, warmth, or itch at or near the injection site) or systemic reactions (fever, nausea, vomiting, diarrhoea, headache, fatigue/malaise, myalgia, arthralgia, or enlarged lymph nodes) within the last 24 hours on days 1 through 7. Warmth and itch will be recorded as presence/absence only (i.e., not graded). The primary endpoint for reactogenicity will be solicited grade 3 or 4 local or systemic reactions within 7 days of vaccination, inclusive.

Table 6. Primary endpoints

Primary Endpoint	Outcome	Timepoint	Population measure	Comparison	Measure of association
i.	Seroresponse (see Table 5)	Day-28 visit	% (95% CI)	Fractional vs. Standard	Difference in %
ii.	Reactogenicity: solicited grade 3 or 4 local or systemic reactions within 7 days of vaccination, inclusive	7 days post-booster	% (95% CI)	NA (descriptive)	NA (descriptive)

All analyses will be conducted separately for the different booster vaccines, amongst all strata combined, and then stratified by the primary series strata (see Strategy for multiple imputation

Multiple imputation will be done using a multivariate imputation model (MICE) and 50 imputations. Covariates in the imputation model will be the same as those specified for imputation under the hypothetical strategy (Section 6.15.1 Implementation of the Hypothetical Strategy). For the binary seroresponse outcome, binding antibody levels will be imputed (rather than the relative increase from baseline or binary seroresponse), and then seroresponse will be derived using the imputed value/s.

Subgroup analyses and tests for interaction).

5.2 SECONDARY ENDPOINTS

Table 7. Secondary immunological endpoints

Secondary Endpoint	Outcome	Timepoint (visit)	Population measure	Comparison	Measure of association
i.	Binding antibodies (IgG), BAU/ml	Day-28	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
ii.	Binding antibodies (IgG), BAU/ml	Month-6	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
iii.	Binding antibodies (IgG), BAU/ml	Month-12	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
iv.	ACE2 Binding inhibition* (wild type), %	Day-28	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
v.	ACE2 Binding inhibition* (wild type), %	Month-6	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
vi.	ACE2 Binding inhibition* (wild type), %	Month-12	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
vii.	ACE2 Binding inhibition* (Omicron), %	Day-28	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
viii.	ACE2 Binding inhibition* (Omicron), %	Month-6	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
ix.	ACE2 Binding inhibition* (Omicron), %	Month-12	Mean (95% CI)	Fractional vs. Standard	Difference in means (95% CI)
x.	Neutralising antibody (wild type), NT_{50}	Day-28	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xi.	Neutralising antibody (wild type), NT_{50}	Month-6	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xii.	Neutralising antibody (wild type), NT_{50}	Month-12	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xiii.	Neutralising antibody (Delta), NT_{50}	Day-28	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xiv.	Neutralising antibody (Delta), NT_{50}	Month-6	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xv.	Neutralising antibody (Delta), NT_{50}	Month-12	GM (95% CI)	Fractional	GMR (95% CI)

				vs. Standard	
xvi.	Neutralising antibody (Omicron), NT_{50}	Day-28	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xvii.	Neutralising antibody (Omicron), NT_{50}	Month-6	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)
xviii.	Neutralising antibody (Omicron), NT_{50}	Month-12	GM (95% CI)	Fractional vs. Standard	GMR (95% CI)

All analyses will be conducted separately for the different booster vaccines, amongst all strata combined, and then stratified by the primary series strata (see

Strategy for multiple imputation

Multiple imputation will be done using a multivariate imputation model (MICE) and 50 imputations. Covariates in the imputation model will be the same as those specified for imputation under the hypothetical strategy (Section 6.15.1 Implementation of the Hypothetical Strategy). For the binary seroresponse outcome, binding antibody levels will be imputed (rather than the relative increase from baseline or binary seroresponse), and then seroresponse will be derived using the imputed value/s.

Subgroup analyses and tests for interaction). GM: Geometric mean. GMR: Geometric mean ratio. *Inhibition of binding between the SARS-CoV-2 receptor binding domain and the host-cell ACE2 receptor by neutralising antibody.

5.3 SAFETY ENDPOINTS

Table 8. Safety endpoints

Safety Endpoint	Outcome	Timepoint	Population measure	Comparison	Measure of association
i.	Any# AE to Day 28 (inclusive)*	28 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
ii.	Any# AE to Day 28 (inclusive)* ^ by severity	28 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
iii.	Any# AE to Day 28 (inclusive)* ^ by causality assessment	28 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
iv.	Any AE to Day 28 (inclusive)* by SOC and severity^	28 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
v.	Duration# of AE to Day 28 (inclusive)* by SOC^	28 days post-booster	Median days {25th – 75th percentile}, min - max	Fractional vs. Standard	Descriptive only
vi.	Day of AE onset (days post-booster) to Day 28 (inclusive)* by SOC^	28 days post-booster	N by Day	Fractional vs. Standard	Descriptive only
vii.	AE to Day 28 (inclusive)* by Outcome**^	28 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
viii.	Medically attended unsolicited AE to Month-3 visit (inclusive)	90 days post-booster	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
ix.	SAE to study-end by SOC and expectedness^	Month-12 visit	Frequency [N (%)]	Fractional vs. Standard	Descriptive only
x.	SAE to study-end by Outcome**^	Month-12 visit	Frequency [N (%)]	Fractional vs. Standard	Descriptive only

#The Safety analysis will only include unsolicited adverse events; solicited adverse events are considered in the Reactogenicity analysis. *Adverse events within 28 days inclusive will be considered, rather than all adverse events prior to the Day-28 visit, which can occur between 28- and 35-days post-booster. **Outcome categories are Resolved, Resolved with sequelae, Ongoing, Fatal and Unknown; denominator is the total number of SAEs rather than the number of participants. ^Recurrent events in the same individual will be counted as a single event (using information from the most severe occurrence); all recurrences will be included in the line list of all adverse events. #Event duration of 'Ongoing' adverse events will be the number of days between onset and the last visit.

5.4 BREAKTHROUGH INFECTION ENDPOINTS

Table 9. Breakthrough infection endpoints

Breakthrough Infection Endpoint	Outcome	Timepoint#	Population measure	Comparison	Measure of association
i.	Breakthrough infection	To Day-28 visit; Month-6	Incidence risk	Fractional vs. Standard	Descriptive only
ii.	Breakthrough infection by time-		Incidence risk	Fractional	Descriptive

	period (<14 days, Day 14 – Day-28 visit, Day-28 visit – Month-6 visit, Month-6 visit – Month-12 visit)	visit; and Month-12 visit		vs. Standard	only
iii.	Breakthrough infection by clinical spectrum (initial infection)*		Incidence risk	Fractional vs. Standard	Descriptive only
iv.	Breakthrough infection		Incidence rate	Fractional vs. Standard	Descriptive only
v.	Breakthrough infection by clinical spectrum*		Incidence rate	Fractional vs. Standard	Descriptive only
vi.	Time to initial breakthrough infection		Survival Curve	Fractional vs. Standard	Descriptive only
vii.	Time to initial breakthrough infection by clinical spectrum*		Survival Curve	Fractional vs. Standard	Descriptive only

*Categorised as Mild, Moderate, Severe, Critical as per Australian guidelines for the clinical care of people with COVID-19: https://app.magicapp.org/#/guideline/L4Q5An/section/nV2P3n #Analysis to be repeated at each analysis timepoint, for the risk and rate of breakthrough infection to that timepoint.

6 STATISTICAL METHODOLOGY

6.1 GENERAL METHODOLOGY

6.1.1 Summary of changes compared to the protocols

- "Functional antibodies" have been described more precisely as "ACE2 binding inhibition by neutralising antibody" in the SAP.
- The SAP added to the definition of seroresponse a specification for participants with binding antibody levels under the limit of detection.
- The "interim analysis" described in the protocol is considered in the SAP as the final analysis of the Day-28 endpoints as the intention is to only conduct this analysis once all Day-28 data is available (no interim analyses are specified in the SAP).
- Grading for hardness and swelling in Mongolia will not consider interference with daily activities as per the protocol as this information is not being captured.
- The protocol does not specify blinding/unblinding of statisticians and data analysts (only specified for participants, those evaluating reactogenicity, vaccinator, immunologists and laboratory staff, clinical investigators); details on blinding of statisticians and data analysts are specified in this SAP.
- In the Mongolia trial protocol, warmth and itch are binary presence/absence variables, with presence falling under Grade 3 and 4 reactions; in the SAP, warmth and itch are to be analysed as binary presence/absence variables with no grading.
- The BCOV22 protocol specifies non-inferiority analyses in terms of seroresponse at Day-28 (from BCOV21), Month-6, and Month-12. The analysis of Day-28 binding antibody data from BCOV21 has already been conducted by the BCOV21 investigators, and this SAP does not specify re-analysis of this data. Further, Month-6 and Month-12 analyses specified in this SAP are based on the superiority framework and will use continuous data only (a binary seroresponse variable will not be considered).

6.1.2 Framework

The primary endpoint is testing for non-inferiority in seroresponse, with a non-inferiority margin of -10%. The secondary endpoints are testing for superiority. The reactogenicity and safety endpoints are descriptive and will be interpreted in conjunction with the results of the primary and secondary endpoints.

6.1.3 Reporting conventions

All applicable statistical tests will be 2-sided and performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

6.1.4 Validation of results

Details of data cleaning and verification, including consistency and range checks, are specified in the Data Management Plan. The analysis of the primary immunological endpoint, including any derivation of outcomes and/or covariates from raw data, will be independently double programmed by two analysts prior to unblinding using a randomly generated dummy variable for treatment allocation; discrepancies in results will be resolved by consensus.

6.1.5 Statistical software

All analyses will be conducted using Stata Version 17.0.

6.1.6 Data management plan

The Data Management Plan will be stored in the Florence eBinder for each trial (Section 12). The version dated May 24th 2022 was used when writing the SAP.

6.1.7 Statistical Master File

Documents relating to the statistical analysis will be store in the Florence eBinder for each trial (Section 15). Documents stored within the Florence eBinder will include this SAP (including evidence of approval/sign-off), statistical reports, and any correspondence related to post-approval SAP amendments.

6.1.8 Reporting

Clinical Study Reports are to be produced for the funder, separately for each trial (Indonesia Trial, BCOV22 Observational Study, and Mongolia Trial). All analyses will be conducted according to the SAP. However, the formatting of figures and tables may be modified, and additional descriptive (but not comparative) statistics provided, to comply with the ICH E3 Guidelines on the Structure and Content of Clinical Study Reports.[1]

6.2 TIMING OF ANALYSES

Due to the rapidly evolving nature of the pandemic, analyses will be conducted for each immunological endpoint once the necessary data have been cleaned and locked, which will be as soon as is practicable after all participants have completed their Day-28 visit (for Day-28 endpoints), Month-6 visit (for Month-6 endpoints), or Month-12 visit (for Month-12 endpoints). Necessary data includes those required for the reactogenicity, safety, and breakthrough infection endpoints, and data on intercurrent events, to the same timepoint as for the immunological endpoint that is to be analysed, as these are essential for interpretation. A list of necessary variables is provided in Section 6.3.

For primary endpoint (i) (comparison of binding antibodies at Day-28 between fractional and standard dose groups), it is estimated that the relevant data will be locked within 8 weeks of the final participant completing their Day-28 visit. The statistical analyses will be conducted within 8 weeks of data locking.

6.3 LIST OF NECESSARY VARIABLES

Below is a list of necessary variables that need to be cleaned and locked for the analysis of each immunological endpoint to be triggered, in addition to the immunological parameter itself:

- Third dose allocation (arm)

- Trial vaccine
- Primary series vaccine strata
- Age group strata
- Dates of first and second doses
- Date of trial vaccine (Day 0)
- Date of blood-draw/study visit
- Reactogenicity for all solicited reactions on 7 days, including grading (Day-28 timepoint only)
- SARS-CoV-2 infection, including clinical spectrum, and date of positive test (to relevant timepoint)
- Receipt of 4th dose (yes/no, and date) (to relevant timepoint)
- Adverse events (severity, causality, SOC, seriousness, expectedness, and outcome) (to relevant timepoint)
- Baseline value of the immunological parameter to be analysed

6.4 INTERIM ANALYSIS

There will be no interim analyses, however the final analyses for each endpoint will be conducted as soon as is practicable after all participants have completed their Day-28 visit (for Day-28 endpoints), Month-6 visit (for Month-6 endpoints), or Month-12 visit (for Month-12 endpoints) (see 6.2 Timing of analyses). An interim report will be prepared for CEPI at the end of 2022, which will include the results for the primary endpoints.

6.5 MULTIPLICITY ADJUSTMENT

For the primary objective, which tests for non-inferiority of a fractional dose compared to the standard dose, for each trial vaccine, no adjustment for multiplicity is necessary as these vaccines are distinct such that a global null hypothesis is not relevant.[2]

Secondary outcome results will be interpreted precisely (including the timepoint and the specific outcome) so that the per-comparison-wise error rate is not increased and adjustment for multiplicity is not required.[3]

6.6 PARTICIPANT DISPOSITION

A CONSORT flow diagram will be used to summarise the study population from screening to analysis, including the number of people who were:

- Screened for eligibility
  - and were eligible at screening
  - and were ineligible at screening (screen failures)*
- Eligible at screening but not randomised*
- Ineligible at screening but randomised (protocol violation)*
- Eligible and randomised

[Subsequent numbers will be given by study group]

- Allocated to each study group
  - and received the allocated vaccine
  - and did not receive the allocated vaccine*
- Included in the Reactogenicity and Safety Population (according to vaccine received not allocated)^
- Included in the Primary Day-28 Immunology Population^
- Included in the Secondary Day-28 Immunology Population^
- Included in the Month-6 Immunology Population^

- Included in the Month-12 Immunology Population^

Reasons will be provided.

^*The number of participants with missing data will be noted (data will be imputed in a sensitivity analysis if missingness is >5%). Missing data arising from lost-to-follow-up or withdrawal will be enumerated, including the level of withdrawal (from intervention, follow-up, or both, and consent to use data up to the time of withdrawal) and reasons (harms-related reasons for withdrawal will be emphasised).*

6.7 PATIENT CHARACTERISTICS AND BASELINE COMPARISONS

Baseline and demographic characteristics, including stratifying variables (primary series and age group) will be described by study group; see Dummy Table 2. Categorical variables will be described with the number in each category and corresponding percentage of the whole study group. Normally distributed continuous variables will be described by the mean, standard deviation, and minimum and maximum values. Non-normally distributed continuous variables will be described by the median, 25th and 75th percentiles, and minimum and maximum values. Statistical tests for differences between study groups at baseline will not be performed.

6.8 ADHERENCE AND PROTOCOL DEVIATIONS

Adherence to the intervention is defined as receiving a trial booster vaccination on Day 0. The number and percent of participants who adhered will be presented by study group.

Pre-defined major protocol deviations (with a direct bearing on the primary outcome) are:

- Receiving a 4th dose prior to the Day-28 visit
- Inclusion and randomisation of an ineligible person
- Receiving the wrong trial vaccination
- Day-28 visit occurring outside of the specified time window (between Day 28 and 35 [inclusive], with Day 0 being the day of trial vaccination)

All protocol deviations will be classified as minor or major prior to unblinding. Major protocol deviations are those that are deemed to significantly affect the rights or safety of a trial participant, or the reliability, accuracy, and robustness of the data. The number and percentage of patients with major and minor protocol deviations will be summarised by study group (as per randomisation), with details of type of deviation provided.

6.9 CONCOMITANT MEDICATIONS

Concomitant medications at baseline and throughout the study period will be described by third dose allocation and priming vaccine stratum. New medications taken during the trial in response to a local or general reaction or an AE will also be recorded. For AEs, the medication taken will be included in a line list of all AEs.

6.10 RESCUE VACCINATION

The protocol specifies that if responses are considered by the DSMB to be inadequate an appropriate rescue strategy will be developed, probably involving a single dose [dosage not specified] of the vaccine in question at 3 months. Rescue vaccination will only be given to participants in the fractional dose groups and will be treated as an intercurrent event using the Treatment Policy strategy, such that the estimand will be a comparison of a standard dose *without rescue vaccination* vs. a fractional dose *with rescue vaccination*

if required for all Month-6 and Month-12 endpoints. Results should be interpreted within the context of the proportion of fractional dose recipients who receive rescue vaccination.

6.11 DEFINITIONS RELATED TO ESTIMANDS

Sections 6.13 'Analysis of the primary endpoints' and 6.14 'Analysis of secondary endpoints' specify analytical approaches for the primary and secondary endpoints using the estimand framework. An estimand is a precise description of the quantity that is estimated to assess the treatment effect reflecting the clinical question posed by a given clinical trial objective. It has 5 attributes: population, treatment, variable of interest e.g., outcome & timepoint, summary measure, and possible intercurrent events (defined as an event that can occur post-randomisation and preclude or affect the interpretation of the variable of interest e.g. discontinuation of treatment). Intercurrent events specific to this trial are described in Section 4.4 'Intercurrent events'.

When defining an estimand, it must be made clear how intercurrent events will be handled in the analysis. Different approaches can be taken towards handling intercurrent events and are described below:

i) Hypothetical: a strategy which envisages a scenario in which the intercurrent event would not occur, e.g., if participants had not switched treatment or if death had not occurred
ii) Treatment policy: a strategy which seeks to understand the treatment effect on the variable regardless of the intercurrent event, i.e., an outcome is of interest whether or not the intercurrent event occurred prior to the outcome, e.g. the final outcome is of interest irrespective of whether the participant takes additional medication
iii) Composite: a strategy which considers the occurrence of the intercurrent event as informative about the participants outcome. Under this strategy the intercurrent event is included in the endpoint definition, e.g., classifying the use of rescue medication as failure, in addition to disease progression, in a time-to-event analysis
iv) Principal Stratification: a strategy wherein treatment effects are assessed in the stratum of participants who would have a specific status with respect to the intercurrent event e.g., examining the effect of treatment in participants who would not require rescue medication
v) While-on-treatment: a strategy which considers response to treatment prior to the occurrence of the intercurrent event to be of interest. For repeated measures, values up to the intercurrent event are of interest but not values after the intercurrent event. Generally, this strategy is only useful if the duration of treatment is not relevant either because it is not clinically relevant or because the rate of an event or outcome is constant over time e.g. the rate of adverse events, where one assumes a constant hazard.

In general, we have leant towards strategies that do not require strong model assumptions (e.g. treatment policy), especially for intercurrent events that are likely to be rare (e.g. breakthrough infections prior to the Day-28 visit). We have specified supplementary analyses that target arguably more relevant estimands that require stronger model assumptions.

Withdrawals/lost-to-follow-up and deaths will be considered as missing data rather than intercurrent events, and will be handled using multiple imputation.[4]

6.12 ESTIMAND-TO-ANALYSIS TABLES

To incorporate the estimand framework into the SAP we use "estimand-to-analysis" tables, as described by Kang, *et al.* 2022:

"The estimand-to-analysis table template starts with the study objective describing the clinical question of interest as written in the trial protocol. The remainder of the table describes each attribute of the estimand (treatment, target population, variable, intercurrent events, and population-level summary) in the left column (ESTIMAND), while the right column describes how each attribute will be handled using the data collected in the clinical trial (ANALYSIS)."[5]

6.13 ANALYSIS OF THE PRIMARY ENDPOINTS

Table 10. Estimand-to-Analysis table[5] for seroresponse at Day-28 (primary immunogenicity endpoint)

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Assess and compare the immune response measured as binding antibodies (IgG) following standard versus fractional doses of either trial vaccine given as a single additional dose to adults 18 years or older in Indonesia/Mongolia who have been primed through previous vaccination with either of the included primary series. (Timepoint – 28 days post vaccination)</td></tr>
<tr><td colspan="2">Estimand (for each trial vaccine):</td><td>The difference in seroresponse proportions 28 days after boosting with a single fractional dose compared to a single standard dose of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of SARS-CoV-2 infection.</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment
Fractional dose (for each trial vaccine)</td><td>Study arms
Interventions (for each trial vaccine): Fractional dose
Comparisons (for each trial vaccine): Standard dose</td></tr>
<tr><td colspan="2">Target population
Adults 18 years or older in Indonesia/Mongolia who have been primed through previous vaccination with one of the included primary series.</td><td>Analysis set (“Primary Day-28 Immunology Population”)
All randomised participants as per randomisation with complete outcome and covariate data</td></tr>
<tr><td colspan="2">Variable
Seroresponse in binding antibodies 28 days after boosting.</td><td>Outcome measure
Seroresponse in binding antibodies at the Day-28 visit (28 – 35 days post-booster), defined as per Table 5.</td></tr>
<tr><td colspan="2">Handling of intercurrent events</td><td rowspan="3">Handling of missing data
The proportion of participants excluded due to missing outcome or covariate data will be described by study group.

If >5% of participants are excluded due to missing data, a supplementary analysis will be performed with multiple imputation (Table 14).</td></tr>
<tr><td>Event (up to and including Day-28 visit)</td><td>Strategy[4]</td></tr>
<tr><td>SARS-CoV-2 infection</td><td>Treatment Policy[#] (interpret results in conjunction with breakthrough infection rates)</td></tr>
<tr><td colspan="2">Population-level summary measure
Difference in seroresponse proportions</td><td>Analysis approach
The difference between proportions will be estimated with 95% confidence intervals using binomial regression (identity link), adjusting for stratifying variables (age group and primary series), duration between 1st and 2nd, and 2nd and 3rd doses, study day of blood draw, and binding antibody level at baseline[6]:
<code>glm [seroresponse] [arm] [age group] [primary series] [days 1st–2nd dose] [days 2nd–3rd dose] [study day of blood draw] [baseline antibody], family(binomial) link(identity)</code>

Results will be interpreted as described in Section 2.3 Framework.</td></tr>
</table>

[#]Supplementary analyses will be conducted using the Hypothetical Strategy for handling intercurrent events (see Table 14).

Table 11. Estimand-to-Analysis[5] table for at least one solicited grade 3 or 4 local or systemic reaction within 7 days of boosting (primary reactogenicity endpoint)

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Assess the rate and severity of reactogenicity within one-week post-booster for each group. (Timepoint – daily, for seven days post vaccination)</td></tr>
<tr><td colspan="2">Estimand:</td><td>Incidence risk of a grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting, by dosage (fractional or standard) and trial vaccine in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series.</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment
Fractional dose (for each trial vaccine)</td><td>Study arms
Interventions (for each trial vaccine): Fractional dose
Comparisons (for each trial vaccine): Standard dose</td></tr>
<tr><td colspan="2">Target population
Adults 18 years or older in Indonesia/Mongolia who have been primed through previous vaccination with one of the included primary series.</td><td>Analysis set (“Reactogenicity Population”)
All participants, as per trial vaccine received (regardless of allocation).</td></tr>
<tr><td colspan="2">Variable
Grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td><td>Outcome measure
Presence of at least one solicited grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td></tr>
<tr><td colspan="2">Handling of intercurrent events</td><td rowspan="4">Handling of missing data
It will be assumed that participants with missing reactogenicity datapoints (collected daily for each reaction type) did not experience the specific reaction on the day/s where the value is missing. Missing data by day and reaction will be described by study group.</td></tr>
<tr><td>Event (up to and including Day-7)</td><td>Strategy[4]</td></tr>
<tr><td>SARS-CoV-2 infection</td><td>While Negative (values up to the day of the first positive test are used)</td></tr>
<tr><td>Death</td><td>While Alive (values up to the time of death are used)</td></tr>
<tr><td colspan="2">Population-level summary measure
Incidence risk (proportion) of at least one solicited grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td><td>Analysis approach
Proportions will be estimated with 95% Clopper-Pearson binomial confidence intervals using the <code>ci</code> Stata command.

Supplementary analysis:
The following reaction-specific descriptive analyses will also be conducted:
• Number and percentage of individuals with each reaction type, presented in a radial graph (Dummy Figure 3).
• Number and percentage of participants with each reaction type, by severity grade (Dummy Figure S 3).
• Distribution of the day of onset for each reaction type
• Distribution of the duration of each reaction type</td></tr>
</table>

6.14 ANALYSIS OF SECONDARY ENDPOINTS

Table 12. Generic Estimand-to-Analysis table for all secondary Day-28 immunological endpoints (specified in Table 7).

Objectives (as per Protocol): Binding antibody endpoints: As per Table 10 Neutralising antibody endpoints: Compare the immunogenicity, both humoral and cellular, over 12 months following fractional and standard booster doses of the vaccines listed.	
Estimand:	[MoA]* of [OUTCOME]* 28 days after boosting with a single fractional dose compared to a single standard dose of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of SARS-CoV-2 infection.
ESTIMAND Attributes:	**Incorporation of Estimand Attribute in ANALYSIS:**
Treatment As per Table 10	**Study arms** As per Table 10
Target population As per Table 10	**Analysis set ("Secondary Day-28 Immunology Population")** All randomised participants as per randomisation with complete outcome and covariate data
Variable [OUTCOME]*, 28 days after boosting.	**Outcome measure** [OUTCOME]* at the Day-28 visit (28 – 35 days post-booster).
Handling of intercurrent events As per Table 10	**Handling of missing data** As per Table 10
Population-level summary measure Geometric mean ratio (GMR) OR Difference in Means*	**Analysis approach** Linear regression will be used to estimate the difference in mean [OUTCOME]* between fractional and standard dose arms, adjusted for stratifying variables (age group and primary series), duration between 1st and 2nd, and 2nd and 3rd doses, study day of blood-draw, and baseline [OUTCOME]* levels. Where the population-level summary measure is the GMR, the outcome variable (and the baseline value) will be $\log_e$ transformed prior to regression, and the GMR (95% CI) will be calculated as the antilogarithms of the mean difference (β_1) and it's 95% CI.

*This table is generic for all secondary Day-28 immunological endpoints (see Table 7), which will be analysed in the same way depending on their distributions; the population measure for outcomes with skewed distributions is the geometric mean and the population-level summary measure of association (MoA) is the GMR – baseline and Day-28 values will be $\log_e$ transformed prior to analysis; the population measure for normally distributed outcomes (ACE2 binding inhibition) is the mean and the population-level summary measure of association (MoA) is the Difference in Means.

Table 13. Generic Estimand-to-Analysis table for all secondary Month-6 and Month-12 immunological endpoints (specified in Table 7).

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Compare the immunogenicity, both humoral and cellular, over 12 months following fractional and standard booster doses of the vaccines listed.</td></tr>
<tr><td colspan="2">Estimand:</td><td>[MoA]* of [OUTCOME]* 6/12 months after boosting with a single fractional dose (with rescue vaccination if required) compared to a single standard dose (without rescue) of either of the COVID-19 trial vaccines, irrespective of breakthrough infections or receipt of a 4th dose (self-initiated).</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment
Fractional dose (for each trial vaccine) with rescue vaccination if required</td><td>Study arms
Interventions (for each trial vaccine): Fractional dose with rescue vaccination if required
Comparisons (for each trial vaccine): Standard dose</td></tr>
<tr><td colspan="2">Target population
As per Table 10</td><td>Analysis set (“Month-6/12 Immunology Population”)
All randomised participants as per randomisation with complete outcome and covariate data</td></tr>
<tr><td colspan="2">Variable
[OUTCOME]*, 6/12 months after boosting.</td><td>Outcome measure
[OUTCOME]* at the Month-6/12 visit (6/12 months +/- 14 days post-booster).</td></tr>
<tr><td colspan="2">Handling of intercurrent events
<table><tr><td>Event (up to and including Month-6/12 visit)</td><td>Strategy[A]</td></tr><tr><td>SARS-CoV-2 infection at any time</td><td>Treatment Policy (interpret results in conjunction with breakthrough infection rates)</td></tr><tr><td>Receipt of 4th dose (self-initiated)</td><td>Treatment Policy (interpret results in conjunction with 4th dose coverage)</td></tr></table></td><td>Handling of missing data
As per Table 10</td></tr>
<tr><td colspan="2">Population-level summary measure
As per Table 12</td><td>Analysis approach
As per Table 12</td></tr>
</table>

*This table is generic for all secondary Month-6 and Month-12 immunological endpoints (see Table 7), which will be analysed in the same way depending on their distributions; the population measure for outcomes with skewed distributions is the geometric mean and the population-level summary measure of association (MoA) is the GMR – baseline and Month-[6/12] values will be $\log_e$ transformed prior to analysis; the population measure for normally distributed outcomes (ACE2 binding inhibition) is the mean and the population-level summary measure of association (MoA) is the Difference in Means.

6.15 SUPPLEMENTARY AND SENSITIVITY ANALYSES

The following supplementary and sensitivity analyses will be conducted. The supplementary analyses use alternative strategies for handling intercurrent events and thus target different estimands; the results will help to fully understand the impact of the intercurrent events and the strategies used to handle them. The sensitivity analyses target the same estimands and test the sensitivity of deviations from assumptions about missing data.[4]

Table 14. Supplementary and Sensitivity Analyses

	MAIN ANALYSIS (Complete Case)		SUPPLEMENTARY ANALYSIS (for IcE Strategy)			SENSITIVITY ANALYSIS (for >5% missingness)
Endpoints	**Estimand**	**IcE & Strategy**	**Change to Estimand from Main Analysis**	**IcE & Strategy**	**Impact**	
Primary immunological endpoint (seroresponse at Day-28)	The difference in seroresponse proportions 28 days after boosting with a single fractional dose compared to a single standard dose of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of SARS-CoV-2 infection.	SARS-CoV-2 infection: Treatment Policy	..., irrespective of SARS-CoV-2 infection ≤ 14 days post-booster, and in a hypothetical scenario in which there were no breakthrough infections on or after Day 15.	SARS-CoV-2 infection ≤ 14 days post-booster: Treatment Policy SARS-CoV-2 infection on or after Day 15: Hypothetical[6]	Imagines a scenario in which breakthrough infections on or after Day 15 did not occur.	The main analysis will be repeated including all participants through multiple imputation (MICE) of missing outcome and covariate data.
Day-28 Secondary immunological endpoints#	[Geometric mean ratio in [OUTCOME] OR Difference in Mean ACE2 binding inhibition]# 28 days after boosting with a single fractional dose compared to a single standard dose of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of SARS-CoV-2 infection.	SARS-CoV-2 infection: Treatment Policy	As above	As above	As above	
Month-[6/12]^ Secondary immunological endpoints#	[Geometric mean ratio in [OUTCOME] OR Difference in Mean ACE2 binding inhibition]# [6/12]^ months after boosting with a single fractional dose (with rescue	SARS-CoV-2 infection: Treatment Policy	..., irrespective of SARS-CoV-2 infection ≤ 14 days post-booster or receipt of a 4th dose	SARS-CoV-2 infection ≤ 14 days post-booster:	As above	

	vaccination if required) compared to a single standard dose (without rescue) of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of breakthrough infections or receipt of a 4th dose (self-initiated).	Self-initiated 4th dose: Treatment Policy	(self-initiated), and in a hypothetical scenario in which there were no breakthrough infections on or after Day 15	Treatment Policy Receipt of 4th dose (self-initiated): Treatment Policy SARS-CoV-2 infection on or after Day 15: Hypothetical[δ]		
Month-[6/12]^ Secondary immunological endpoints[#]	Geometric mean ratio in [OUTCOME] OR Difference in Mean ACE2 binding inhibition][#] [6/12]^ months after boosting with a single fractional dose (with rescue vaccination if required) compared to a single standard dose (without rescue) of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series, irrespective of breakthrough infections or receipt of a 4th dose (self-initiated).	SARS-CoV-2 infection: Treatment Policy Self-initiated 4th dose: Treatment Policy	..., irrespective of SARS-CoV-2 infection), and in a hypothetical scenario in which no participants received a self-initiated 4th dose.	SARS-CoV-2 infection: Treatment Policy Receipt of 4th dose (self-initiated): Hypothetical[δ]	Imagines a scenario in which no participants received a self-initiated 4th dose.	
Month-[6/12]^ Secondary immunological endpoints[#]	Geometric mean ratio in [OUTCOME] OR Difference in Mean ACE2 binding inhibition][#] [6/12]^ months after boosting with a single fractional dose (with rescue vaccination if required) compared to a single standard dose (without rescue) of either of the COVID-19 trial vaccines in adults 18 years or older in [Indonesia/Mongolia] who have been primed through previous vaccination with either of the included primary series,	SARS-CoV-2 infection: Treatment Policy Self-initiated 4th dose: Treatment Policy	..., irrespective of SARS-CoV-2 infection ≤ 14 days post-booster, and in a hypothetical scenario in which: - there were no breakthrough infections on or after Day 15, AND; -no participants received a self-initiated	SARS-CoV-2 infection ≤ 14 days post-booster: Treatment Policy SARS-CoV-2 infection on or after Day 15: Hypothetical[δ]	Imagines a scenario in which: -breakthrough infections on or after Day 15 did not occur. AND	

	irrespective of breakthrough infections or receipt of a 4th dose (self-initiated).		4th dose.	Receipt of 4th dose (self-initiated): Hypothetical[δ]	-no participants received a self-initiated 4th dose	

#This row is generic for all immunological endpoints at the specified timepoint (Table 7). The specified supplementary analyses will be conducted for each endpoint, separately for each trial vaccine. ^This row is generic for the Month-6 and Month-12 timepoints. [δ]Under the hypothetical strategy, outcome values experienced after the specified intercurrent events will be set to missing and multiple imputation will be used to calculate the estimate including these participants. The parts of the Estimands and intercurrent event strategies that are being modified in the each of supplementary analyses are highlighted by blue text.

6.15.1 Implementation of the Hypothetical Strategy

Under the hypothetical strategy, outcome values experienced after the specified intercurrent events will be set to missing and multiple imputation will be used to calculate the estimate including these participants. For the binary seroresponse outcome, binding antibody levels at Day 28 will be imputed, and then seroresponse will be derived using the imputed value. Multiple imputation will be done using a univariate regression imputation model (logistic regression for binary outcomes and linear regression for continuous outcomes) and 50 imputations. Covariates in the imputation model will be:

- trial vaccine
- study arm (fractional/standard)
- primary series vaccine
- age group
- duration between 1st and 2nd
- duration between 2nd and 3rd doses
- study day of blood draw
- baseline levels of the outcome variable (for seroresponse, baseline binding antibody as a continuous variable will be included).
- For Month-6 and Month-12 endpoints, levels of the outcome variable at previous blood draws will also be included if the intercurrent event occurred after these visits.

6.15.2 Strategy for multiple imputation

Multiple imputation will be done using a multivariate imputation model (MICE) and 50 imputations. Covariates in the imputation model will be the same as those specified for imputation under the hypothetical strategy (Section 6.15.1 Implementation of the Hypothetical Strategy). For the binary seroresponse outcome, binding antibody levels will be imputed (rather than the relative increase from baseline or binary seroresponse), and then seroresponse will be derived using the imputed value/s.

6.16 SUBGROUP ANALYSES AND TESTS FOR INTERACTION

Analyses will be conducted separately for each study (the Indonesia Trial, BCOV22 [concatenated with BCOV21], and the Mongolia Trial). Analyses will also be conducted on concatenated data of the Indonesia Trial and BCOV21/22.

Analyses for all endpoints will be conducted separately for the different booster vaccines, amongst all strata combined. Subgroup analyses by the primary series strata will also be conducted for the primary endpoints, and all binding antibody, ACE2 binding inhibition, safety and breakthrough infection secondary endpoints. Tests of interaction will be done for the primary immunogenicity endpoint and secondary endpoint (i) (see 5.2 Secondary) by fitting a model with an interaction parameter between study arm and primary series strata.

6.17 ANALYSIS OF SAFETY ENDPOINTS

Analyses for all safety endpoints (5.3 Safety endpoints) will be amongst all randomised participants according to the trial vaccine received (the "Safety Population"). Recurrent events in the same individual will be counted as a single event (using information from the most severe occurrence); all recurrences will be included in the line list of all adverse events. Population measures for all safety endpoints (5.3 Safety endpoints) will be reported separately for standard and fractional dose groups, by trial vaccine. Analyses of all safety endpoints will be descriptive only. Missing data on severity, onset, SOC, causality, SAE outcome, and SAE expectedness will be described by study group.

In addition, a list of all adverse events will be provided by third dose allocation, trial vaccine, and primary series vaccine, including the following parameters:

- the patient identifier
- age
- sex
- weight
- height
- adverse event (reported term, lower-level term, and SOC)
- day of onset (from Day 0)
- days since receipt of 4th COVID-19 vaccine dose (self-initiated or as rescue) (if applicable)
- duration (in days)
- severity grade
- seriousness (serious/non-serious)
- special interest (yes/no)
- expectedness (yes/no)
- action taken
- outcome (Resolved, Resolved with sequelae, Ongoing, Fatal and Unknown)
- causality assessment/relatedness *(noting 'adverse reactions' and 'serious adverse reactions')*
- concomitant medication at baseline
- concomitant medication during study (prior to event)
- concomitant medication in response to event
- comorbidities at baseline
- brief narrative (SAEs only)

6.18 ANALYSIS OF BREAKTHROUGH INFECTIONS

Table 15. Generic Estimand-to-Analysis table for all breakthrough infection endpoints for incidence risk (specified in Table 9).

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Identify any difference in the risk of clinically significant COVID-19 cases between any of the study groups [Indonesia Trial and BCOV22]; Evaluate the safety of the booster dose regimens [all studies]</td></tr>
<tr><td colspan="2">Estimand (for each trial vaccine):</td><td>Incidence risk of [OUTCOME]* to [TIMEPOINT]*, by dosage (fractional or standard) and trial vaccine in adults 18 years or older in Indonesia who have been primed through previous vaccination with one of the included primary series.</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment
Fractional dose (for each trial vaccine)</td><td>Study arms
Interventions (for each trial vaccine): Fractional dose
Comparisons (for each trial vaccine): Standard dose</td></tr>
<tr><td colspan="2">Target population
Adults 18 years or older in Indonesia/Mongolia who have been primed through previous vaccination with one of the included primary series.</td><td>Analysis set
All randomised participants</td></tr>
<tr><td colspan="2">Variable
SARS-CoV-2 infection (breakthrough infection)</td><td>Outcome measure
At least one positive SARS-CoV-2 test (PCR)</td></tr>
<tr><td colspan="2">Handling of intercurrent events</td><td rowspan="3">Handling of missing data
Active surveillance for SARS-CoV-2 is not being done. Therefore, participants without a positive SARS-CoV-2 test will be included in the analysis under the assumption that they have not had a breakthrough infection.</td></tr>
<tr><td>Event</td><td>Strategy[4]</td></tr>
<tr><td>Receipt of 4th dose (self-initiated)</td><td>Treatment Policy (interpret results in conjunction with 4th dose coverage)</td></tr>
<tr><td>Receipt of 4th dose (rescue)</td><td>Treatment Policy (interpret results in conjunction with extent of rescue vaccination)</td><td></td></tr>
<tr><td colspan="2">Population-level summary measure
Incidence risk (proportion positive)</td><td>Analysis approach
The incidence risk (a proportion) will be estimated in each group (arm [fractional or standard] and trial vaccine) with 95% CI using the <code>proportion</code> command in Stata.
Analyses are descriptive only (no comparisons between arms will be made).</td></tr>
</table>

*This table is generic for all breakthrough infection endpoints for incidence risks (with varying combinations of outcomes & timepoints) specified in Table 9 as they will be analysed in the same way.

Table 16. Generic Estimand-to-Analysis table for all breakthrough infection endpoints for incidence rate (specified in Table 9).

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Identify any difference in the risk of clinically significant COVID-19 cases between any of the study groups [Indonesia Trial and BCOV22]; Evaluate the safety of the booster dose regimens [all studies]</td></tr>
<tr><td colspan="2">Estimand (for each trial vaccine):</td><td>Incidence rate of [OUTCOME]* to [TIMEPOINT]*, by dosage (fractional or standard) and trial vaccine in adults 18 years or older in Indonesia who have been primed through previous vaccination with one of the included primary series.</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment
Fractional dose (for each trial vaccine)</td><td>Study arms
Interventions (for each trial vaccine): Fractional dose
Comparisons (for each trial vaccine): Standard dose</td></tr>
<tr><td colspan="2">Target population
Adults 18 years or older in Indonesia/Mongolia who have been primed through previous vaccination with one of the included primary series.</td><td>Analysis set
All randomised participants</td></tr>
<tr><td colspan="2">Variable
SARS-CoV-2 infection (breakthrough infection)</td><td>Outcome measure
Positive SARS-CoV-2 test (PCR) (multiple infections within one participant are counted)</td></tr>
<tr><td colspan="2">Handling of intercurrent events
Event | Strategy[4]
Receipt of 4th dose (self-initiated) | Treatment Policy (interpret results in conjunction with 4th dose coverage)
Receipt of 4th dose (rescue) | Treatment Policy (interpret results in conjunction with extent of rescue vaccination)</td><td>Handling of missing data
Active surveillance for SARS-CoV-2 is not being done. Therefore, participants without a positive SARS-CoV-2 test will be included in the analysis as being negative. Participants lost to follow up will be censored at their last visit.</td></tr>
<tr><td colspan="2">Population-level summary measure
Incidence rate per 1000 person years</td><td>Analysis approach
Participants will be considered at risk from Day 0 and censored on the day of the last study visit that was attended; participants will also be censored from the day of a positive SARS-CoV-2 test but will re-enter after 28 days. Failure will be a positive SARS-CoV-2 test, and multiple failures will be allowed in a single participant. The incidence rate per 1000 person-years will be estimated in each group (arm [fractional or standard] and trial vaccine) with 95% CI using the <code>strate</code> command in Stata, after declaring the data as survival data and specifying person-time at risk and the failure variable using the <code>stset</code> command. Analyses are descriptive only (no comparisons between arms will be made).</td></tr>
</table>

*This table is generic for all breakthrough infection endpoints for incidence rates (with varying combinations of outcomes & timepoints) specified in Table 9 as they will be analysed in the same way.

7 PLANNED TABLES AND FIGURES

7.1 PLANNED TABLES AND FIGURES

Main		**Dummy Table**
Table 1	Summary of trial vaccines	Dummy Table 1
Figure 1	CONSORT diagram	Dummy Figure 1
Table 2	Baseline characteristics by third dose allocation	Dummy Table 2
Figure 2	Seroresponse rate at Day-28 between fractional and standard dose groups, by third dose vaccine allocation (primary endpoint)	Dummy Figure 2
Figure 3	Radial graph for solicited grade 3 or 4 local and systemic reactions within 7 days of boosting, inclusive, by third dose allocation	Dummy Figure 3
Table 3	Immune responses at Day-28 by third dose allocation	Dummy Table 3
Table 4	Immune responses at Month-6 by third dose allocation and priming vaccine	Dummy Table 3
Table 5	Immune responses at Month-12 by third dose allocation and priming vaccine	Dummy Table 3
Supplement		
Table S1	Baseline characteristics by third dose allocation, stratified by primary series	Dummy Table 2, split by primary series
Table S2	Proportion of participants who received a 4th dose during the study period	Dummy Table S 1
Figure S1	Seroresponse rate at Day-28 between fractional and standard dose groups, by third dose vaccine allocation and primary series	Dummy Figure S 1
Figures S2	Radial graph for solicited grade 3 or 4 local and systemic reactions within 7 days of boosting, inclusive, by third dose allocation and primary series	Dummy Figure S 2
Figure S3	Distribution of [immunological parameter] at baseline and Day-28 [and Month-6 and Month-12], by third dose allocation and primary series	Box and whisker plot showing median, 25th percentile, 75th percentile, min and max. Repeat for each immunological parameter.
Figure S4	Percentage of individuals with each reaction and severity grade, for each schedule.	Dummy Figure S 3
Table S3	Immune responses at Day-28 by third dose allocation and primary series	Dummy Table S 2
Table S4	Frequency and outcomes of unsolicited adverse events and serious adverse events	Dummy Table S 3

Figure S5	Frequency of unsolicited adverse events to Day 28 (inclusive) by SOC and severity	Dummy Figure S 4
Figure S6	Day of unsolicited AE onset (days post-booster) to Day 28 (inclusive) by SOC	Dummy Figure S 5
Table S5	Line list of all unsolicited adverse events	-
Text	Summary of protocol violations	-
Table S6	Clinical observations prior to trial vaccination	-
Table S7	Concomitant medications (regular medications at baseline)	-

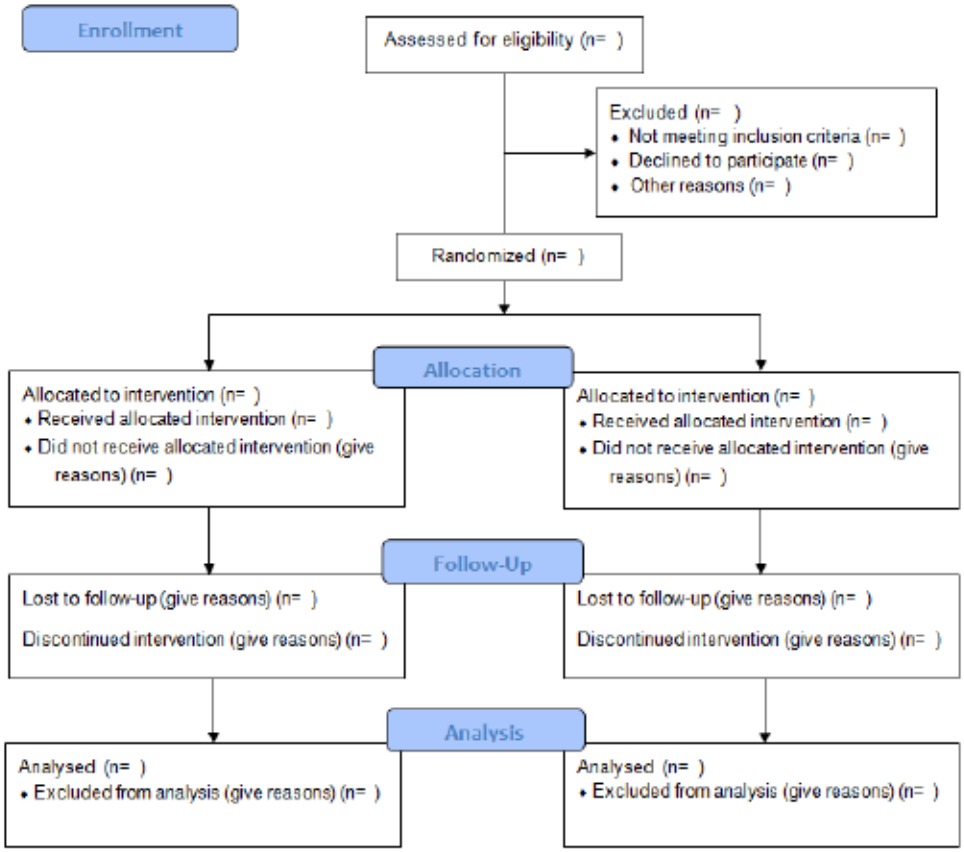
7.1.1 Dummy Tables and Figures – Main

Dummy Table 1. Summary of trial vaccines

Study Group	**Generic vaccine name**	**Route**	**Dose**
Comirnaty® standard full dose	Pfizer-BioNTech (BNT162b2)	Intramuscular	30µg
Comirnaty® fractional dose	Pfizer-BioNTech (BNT162b2)	Intramuscular	15µg
…Add rows for each trial vaccine & arm…			

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

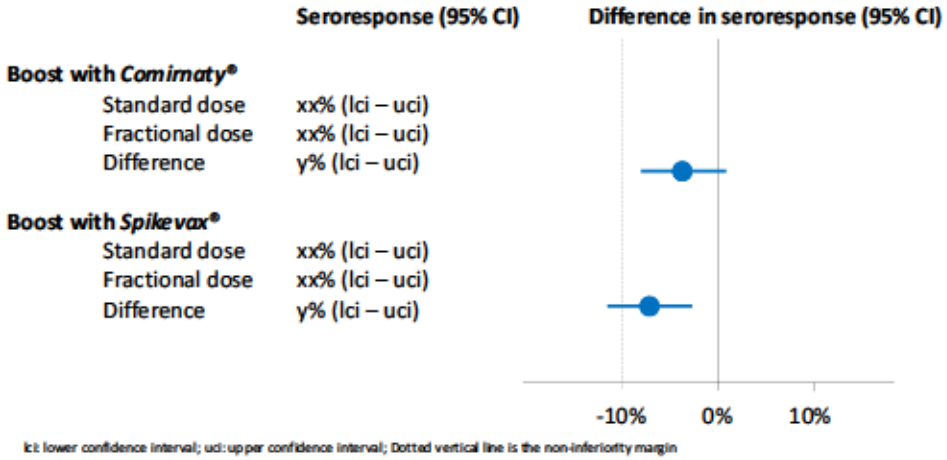


Dummy Figure 1. CONSORT Flow Diagram

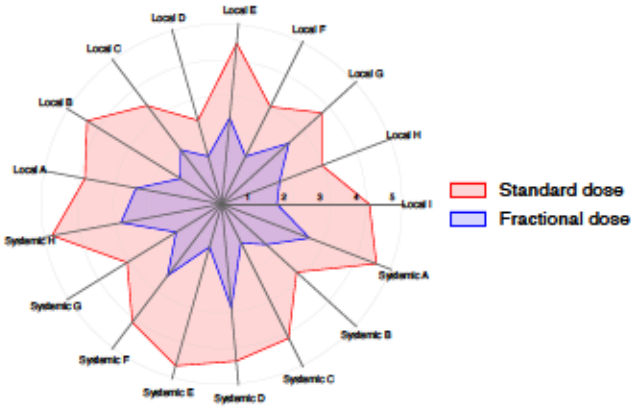
Dummy Table 2. Baseline characteristics by third dose allocation

	Boost with *Comirnaty®*			
	Total (N = n)	Standard Dose (N = n)	Fractional Dose (N = n)	Additional columns will be added for *Spikevax®* and *Vaxzevria®* groups in Indonesia
Age, years	Mean [SD] or Median {IQR}, min-max	Mean [SD] or Median {IQR}, min-max	Mean [SD] or Median {IQR}, min-max	
Age groups, years				
<50	N (%)	N (%)	N (%)	
≥50	N (%)	N (%)	N (%)	
Gender				
Female	N (%)	N (%)	N (%)	
Male	N (%)	N (%)	N (%)	
Interval between 1st and 2nd dose, days	Median {IQR}, min-max	Median {IQR}, min-max	Median {IQR}, min-max	
Interval between 2nd and 3rd	Median {IQR}, min-max	Median {IQR}, min-max	Median {IQR}, min-max	

dose, days				
Reaction to primary series	N (%)	N (%)	N (%)	
Highest level of medical care sought for reaction to primary series	N (%)	N (%)	N (%)	
No care/advice sought	N (%)	N (%)	N (%)	
Pharmacy	N (%)	N (%)	N (%)	
GP	N (%)	N (%)	N (%)	
Emergency Department	N (%)	N (%)	N (%)	
Admitted to Hospital	N (%)	N (%)	N (%)	
Other	N (%)	N (%)	N (%)	
Comorbidities	N (%)	N (%)	N (%)	
Diabetes mellitus	N (%)	N (%)	N (%)	
Gestational diabetes	N (%)	N (%)	N (%)	
Cardiovascular disease	N (%)	N (%)	N (%)	
Hypertension	N (%)	N (%)	N (%)	
Cancer	N (%)	N (%)	N (%)	
Chronic obstructive pulmonary	N (%)	N (%)	N (%)	
Chronic kidney disease	N (%)	N (%)	N (%)	
Chronic liver disease	N (%)	N (%)	N (%)	
Anaphylaxis (or carries an EpiPen)	N (%)	N (%)	N (%)	
Neurological disease (including stroke)	N (%)	N (%)	N (%)	
Anticoagulant therapy	N (%)	N (%)	N (%)	
Immunocompromised	N (%)	N (%)	N (%)	
Mastocytosis causing recurrent anaphylaxis	N (%)	N (%)	N (%)	
Cigarette user	N (%)	N (%)	N (%)	
Currently pregnant	N (%)	N (%)	N (%)	



Dummy Figure 2. Seroresponse rate at Day-28 between fractional and standard dose groups (primary endpoint), by trial vaccine



Dummy Figure 3. Radial graph for solicited grade 3 or 4 local and systemic reactions within 7 days of boosting, inclusive, by trial vaccine *[there will be one radial graph for each trial vaccine – i.e. 3 in Indonesia and 1 in Mongolia]*

Dummy Table 3. Immune responses at <<Day-28/Month-6/Month-12>> by third dose allocation

	Boost with *Comirnaty®*		
	Standard (N = n)	Fractional (N = n)	
Binding Antibodies (IgG), BAU/mL			
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	Additional columns will be added for *Spikevax®* and *Vaxzevria®* groups in Indonesia
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	
ACE2 Binding* inhibition by neutralising antibody (wild type), %			
Mean	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	
MD	Ref	x (x-x)	
ACE2 Binding* inhibition by neutralising antibody (Delta), %			

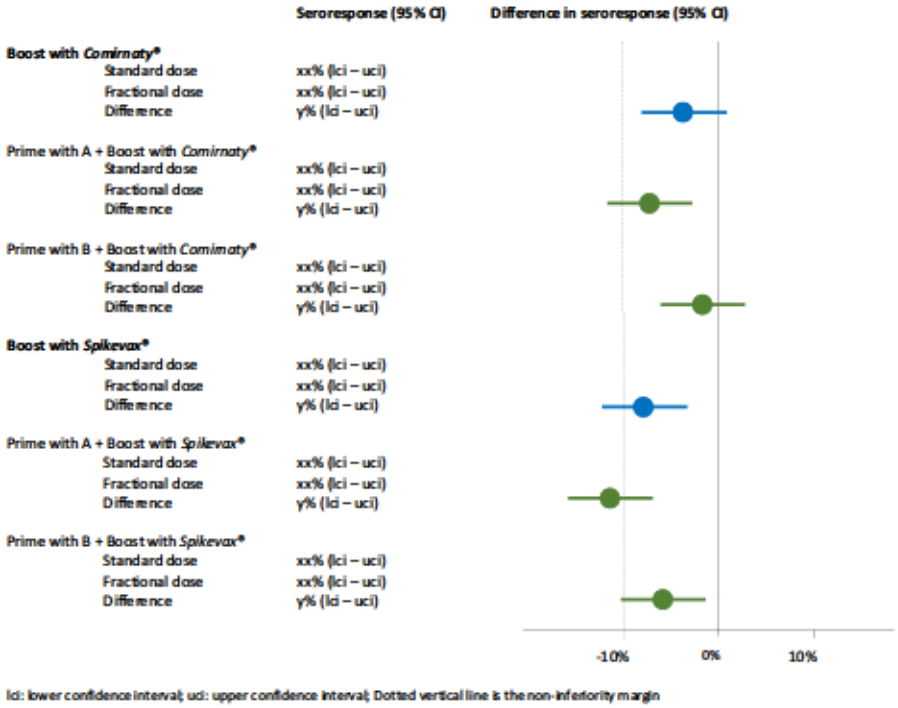
Mean	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	
MD	Ref	x (x-x)	
Neutralising antibody (wild type), NT_{50}			
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	
Neutralising antibody (Delta), NT_{50}			
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	
Neutralising antibody (Omicron), NT_{50}			
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	
IFNγ, IU/ml			
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	
IFNγ-producing cells, cells/million PBMCs			
GM (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	

GMT: Geometric mean titre; GMR: geometric mean ratio; GM: geometric mean; MD: difference in means; Ref: Reference group. *Inhibition of binding between the SARS-CoV-2 receptor binding domain and the host-cell ACE2 receptor by neutralising antibody.

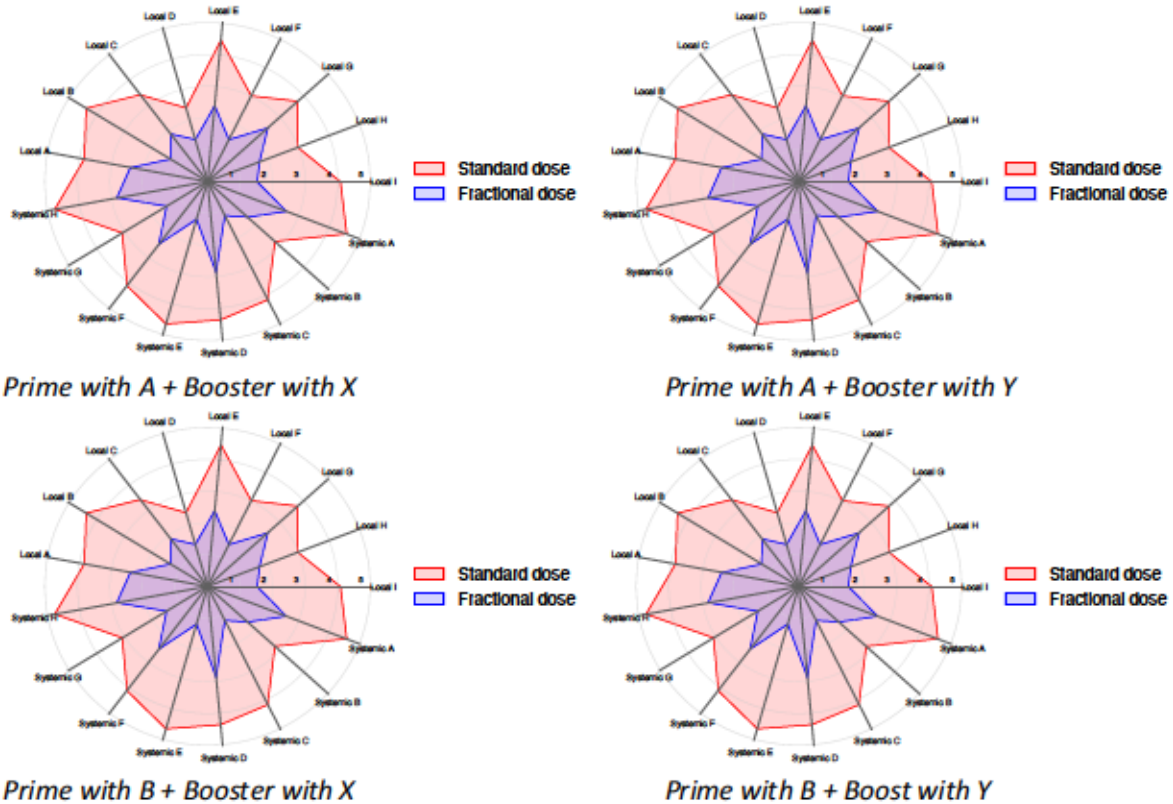
7.1.2 Dummy Tables and Figures - Supplement

Dummy Table S 1. Proportion of participants who received a 4th dose during the study period

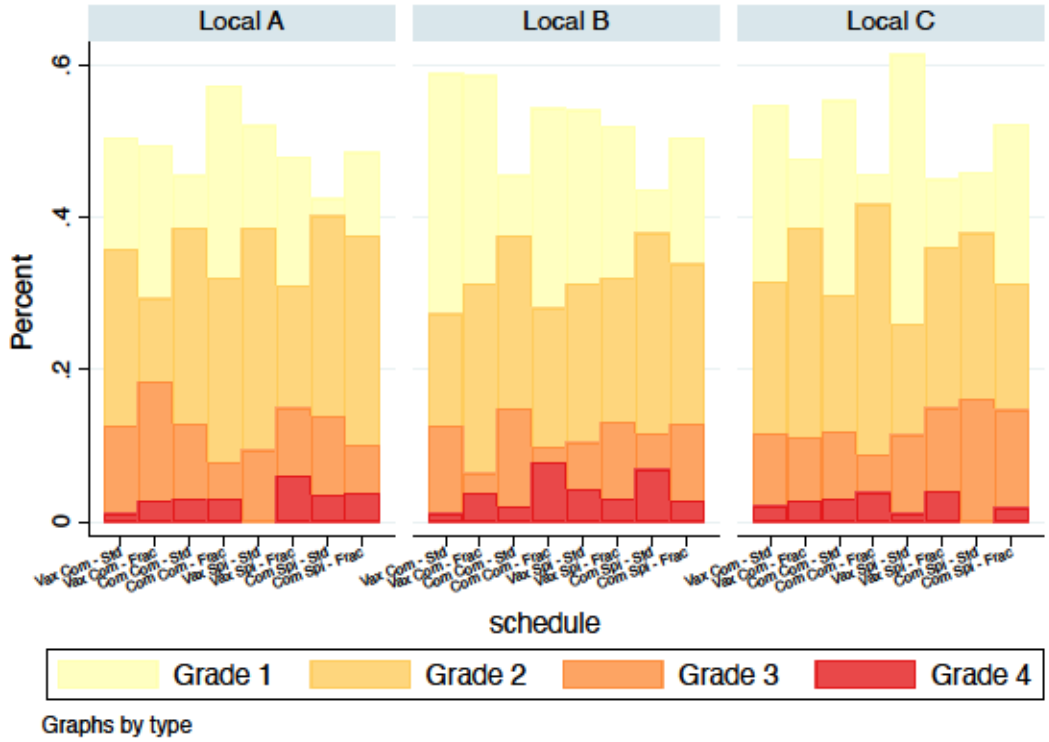
	Prime with *Vaxzevria*®				Prime with *Comirnaty*®			
	Boost with *Comirnaty*®		Boost with *Spikevax*®		Boost with *Comirnaty*®		Boost with *Spikevax*®	
	Standard (N = n)	Fractional (N = n)	Standard (N = n)	Fractional (N = n)	Standard (N = n)	Fractional (N = n)	Standard (N = n)	Fractional (N = n)
Received 4th dose	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Before Month-6 visit, self-initiated	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Before Month-6 visit, as rescue	-	N (%)	-	N (%)	-	N (%)	-	N (%)
After Month-6 visit, self-initiated	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)



Dummy Figure S 1. Seroresponse rate at Day-28 between fractional and standard dose groups, by trial vaccine and primary series



Dummy Figure S 2. Radial graph for solicited grade 3 or 4 local and systemic reactions within 7 days of boosting, inclusive, by trial vaccine and primary series



Dummy Figure S 3. Dummy figure to show the percentage of individuals with each reaction and severity grade, for each schedule.

Dummy Table S 2. Immune responses at <<Day-28/Month-6/Month-12>> by third dose allocation and primary series

	Prime with *A*®				
	Boost with *X*®		Boost with *Y*®		
	Standard (N = n)	Fractional (N = n)	Standard (N = n)	Fractional (N = n)	
Binding Antibodies (IgG), BAU/mL					
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	Additional columns will be added for all unique combinations of primary series and trial vaccine
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	Ref	x.xx (x.xx-x.xx)	
ACE2 Binding* inhibition by neutralising antibody (wild type), %					
Mean	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	
MD	Ref	x (x-x)	Ref	x (x-x)	
ACE2 Binding* inhibition by neutralising antibody (Delta), %					
Mean	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	xx (xx-xx; n=xx)	
MD	Ref	x (x-x)	Ref	x (x-x)	
Neutralising antibody (wild type), NT_{50}					
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR	Ref	x.xx	Ref	x.xx	

(95% CI)		(x.xx-x.xx)		(x.xx-x.xx)	
Neutralising antibody (Delta), NT_{50}					
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	Ref	x.xx (x.xx-x.xx)	
Neutralising antibody (Omicron), NT_{50}					
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	Ref	x.xx (x.xx-x.xx)	
IFNγ, IU/ml					
GMT (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	Ref	x.xx (x.xx-x.xx)	
IFNγ-producing cells, cells/million PBMCs					
GM (95% CI)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	xxx (xxx-xxx; n=xx)	
GMR (95% CI)	Ref	x.xx (x.xx-x.xx)	Ref	x.xx (x.xx-x.xx)	

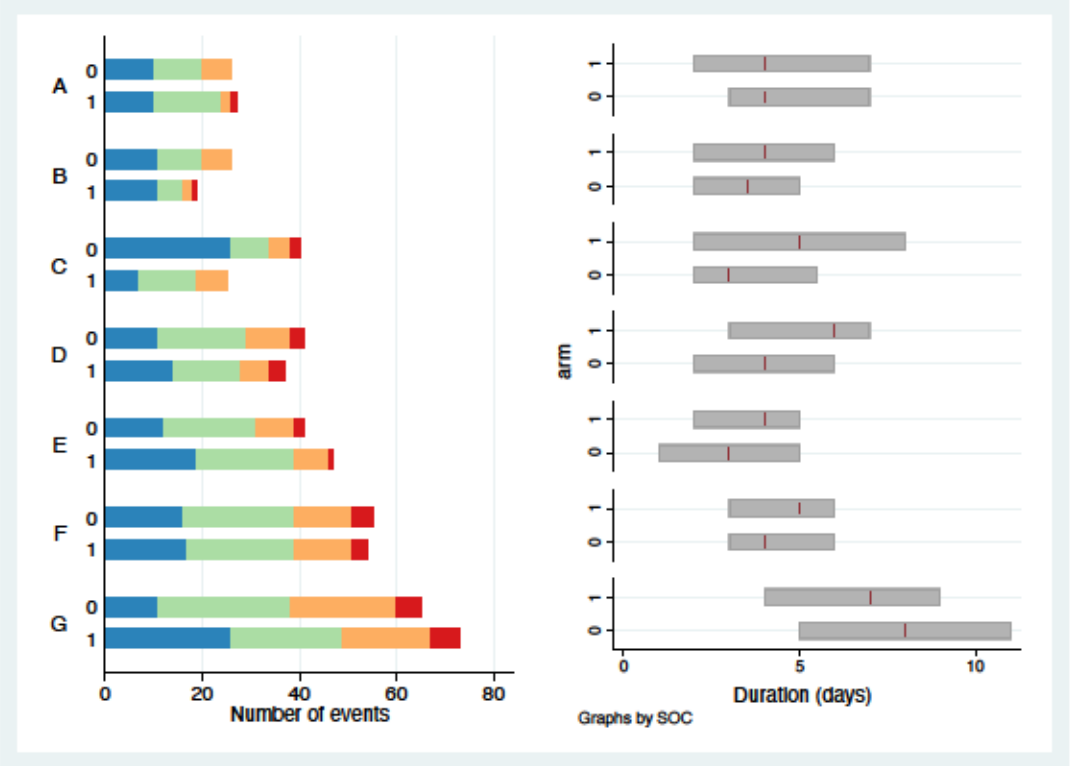
GMT: Geometric mean titre; GMR: geometric mean ratio; GM: geometric mean; MD: difference in means; Ref: Reference group. *Inhibition of binding between the SARS-CoV-2 receptor binding domain and the host-cell ACE2 receptor by neutralising antibody.

Dummy Table S 3. Frequency and outcomes of unsolicited adverse events and serious adverse events

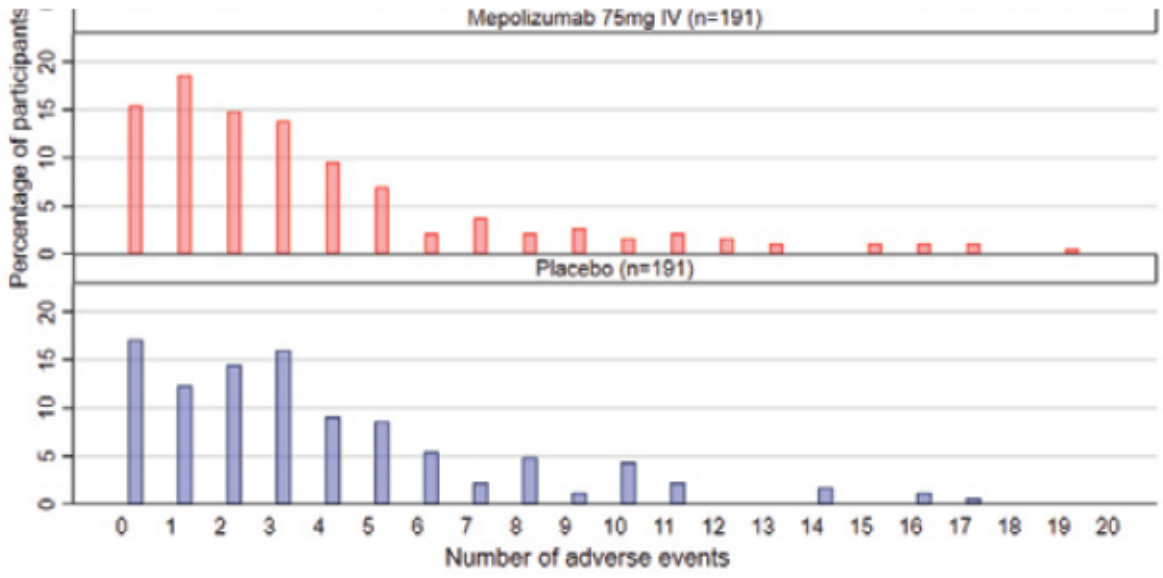
	Boost with *Comirnaty®*			
	Total (N = n)	Standard (N = n)	Fractional (N = n)	Additional columns will be added for *Spikevax®* and *Vaxzevria®* groups in Indonesia
Any AE to Day 28 (inclusive)*	N (%)	N (%)	N (%)	
Any Grade 3 - 5 AE to Day 28 (inclusive)*^	N (%)	N (%)	N (%)	
AE Outcome#				
Resolved	N (%)	N (%)	N (%)	
Resolved with sequelae	N (%)	N (%)	N (%)	
Ongoing	N (%)	N (%)	N (%)	
Fatal	N (%)	N (%)	N (%)	
Unknown	N (%)	N (%)	N (%)	
Medically attended AE to Month-3 visit (inclusive)	N (%)	N (%)	N (%)	
Any SAE to study-end^				
SOC A	N (%)	N (%)	N (%)	
SOC B	N (%)	N (%)	N (%)	
SOC C	N (%)	N (%)	N (%)	
... for all SOCs ...	N (%)	N (%)	N (%)	
SAE Outcome#				
Resolved	N (%)	N (%)	N (%)	
Resolved with sequelae	N (%)	N (%)	N (%)	
Ongoing	N (%)	N (%)	N (%)	
Fatal	N (%)	N (%)	N (%)	
Unknown	N (%)	N (%)	N (%)	

*Unsolicited Adverse events within 28 days inclusive will be considered, rather than all adverse events prior to the Day-28 visit, which can occur between 28- and 35-days post-booster. ^Recurrent events in the same individual will be

counted as a single event (using information from the most severe occurrence); all recurrences will be included in the line list of all adverse events. #Denominator is the total number of AEs/SAEs rather than the number of participants.



Dummy Figure S 4. Frequency of unsolicited adverse events to Day 28 (inclusive) by SOC and severity, and event duration. A – G are different SOCs. Colours represent event severity (Blue=Mild; Red = Severe). [Note: *This type of figure will be generated separately for each trial vaccine and presented in panels within a single figure.*]



Dummy Figure S 5. Onset (days post-booster) of unsolicited AE to Day 28 (inclusive) by SOC. Dummy figure is from Phillips *et al.* 2022.[7] X-axis will be the day of onset rather than the number of adverse events. Mepolizumab and Placebo correspond to Fractional and Standard Dose groups. *[Note: This type of figure will be generated separately for each trial vaccine and SOC and presented in panels within a single figure.]*

8 REFERENCES

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5 Kang M, Kendall MA, Ribaudo H, *et al.* Incorporating estimands into clinical trial statistical analysis plans. *Clin Trials* 2022. DOI:10.1177/17407745221080463.

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