

# PROTOCOL

A randomised controlled trial to assess the immunogenicity as well as safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccine (Pfizer-BioNTech) given as a booster dose after priming with Sinopharm, AstraZeneca or Sputnik in healthy adults in Mongolia.

---

Protocol Number: 81800  
Protocol Version 7.0,  
20 September 2023

## CONFIDENTIAL

This protocol is confidential and is the property of Murdoch Children's Research Institute. No part of it may be transmitted, reproduced, published, or used without prior written authorisation from the institution.

### Statement of Compliance

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity

**CONTENTS**

PROTOCOL SYNOPSIS .....	6
GLOSSARY OF ABBREVIATIONS.....	10
INVESTIGATOR AGREEMENT .....	11
1. ADMINISTRATIVE INFORMATION .....	12
1.1. Trial registration .....	12
1.1.1. Trial registry.....	12
1.2. Sponsor .....	12
1.3. Expected duration of study .....	12
1.4. Contributorship .....	12
1.5. Stakeholder involvement.....	13
2. INTRODUCTION AND BACKGROUND .....	13
2.1. Trial rationale and aim.....	13
2.2. Background .....	14
2.3. Risk/Benefit assessment.....	15
2.3.1. Known potential risks .....	15
2.3.2. Assessment of potential risks and benefits .....	16
2.3.1. Known potential benefits .....	16
3. TRIAL OBJECTIVES AND OUTCOMES .....	16
3.1 Objectives.....	16
3.1.1 Primary objectives .....	16
3.1.2 Secondary objectives.....	16
3.2 Outcomes .....	17
4 TRIAL DESIGN .....	20
4.1 Overall design.....	20
4.2 Justification for dose .....	21
4.3 Trial population .....	21
4.4 Eligibility criteria .....	21
4.4.1 Inclusion criteria .....	21
4.4.2 Exclusion criteria .....	22
4.5 Lifestyle considerations .....	22
4.6 Screen failures.....	22
4.7 Recruitment and identification of potential participants .....	22

4.8	Consent .....	23
5	INTERVENTION .....	23
5.1	Treatment arms.....	23
5.2	Trial Intervention(s).....	23
5.2.1	Description of trial investigational products.....	23
5.2.1.1	Trial Products .....	23
5.2.2	Dosage.....	24
5.2.3	Dose modification .....	24
5.2.4	Storage, preparation, dispensing and administration of trial drug.....	24
5.2.5	Product accountability.....	24
5.2.6	Excluded medications and treatments .....	25
5.2.7	Concomitant therapy .....	25
5.2.8	Discontinuation from trial intervention.....	25
6	RANDOMISATION AND BLINDING .....	25
6.1	Concealment mechanism .....	25
6.2	Breaking of the trial blind .....	26
6.2.1	On trial.....	26
7	TRIAL VISITS AND PROCEDURES .....	26
7.1	Schedule of assessments.....	26
7.2	Description of procedures .....	28
7.2.1	Visit 2 (Day 1) .....	28
7.2.2	Visit 3 (Day 7) .....	28
7.2.3	Visit 4 (Day 28) .....	29
7.2.4	Visit 5 (3 Months) .....	29
7.2.5	Visit 6 (6 Months) .....	29
7.2.6	Visit 7 (12 Months) .....	29
7.2.7	Unscheduled visits.....	30
7.2.8	Withdrawal of consent - participant withdraws from all trial participation .....	30
7.2.9	Losses to follow-up.....	31
7.2.10	Replacements .....	31
7.2.11	Trial Closure.....	31
8	SAFETY MONITORING AND REPORTING .....	31
8.1.1	Definitions for use in trials involving investigational medicinal products.....	31

8.2	Capturing and eliciting adverse event/reaction information.....	32
8.3	Documentation of AEs.....	33
8.4	Assessing the relatedness (causality) of a participant’s AE.....	33
8.6	Reporting of safety events.....	34
9	DATA AND INFORMATION MANAGEMENT .....	35
9.1	Data management.....	35
9.1.1	Data generation (source data).....	35
9.1.2	Data capture methods and data use, storage, access, and disclosure during the trial.....	36
9.1.3	Data confidentiality .....	37
9.1.4	Quality assurance .....	38
9.1.5	Archiving - Data and document retention .....	39
10	TRIAL OVERSIGHT .....	39
10.1	Governance structure.....	39
10.1.1	Trial Management Group (TMG) .....	39
10.1.2	Trial Steering Committee (TSC) .....	39
10.1.3	Safety Monitoring.....	40
10.2	Site Monitoring.....	40
10.3	Quality Control and Quality Assurance.....	40
11	STATISTICAL METHODS .....	41
11.1	Sample Size Estimation.....	41
11.2	Population to be analysed .....	41
11.3	Methods of analysis.....	42
11.4	Interim Analyses .....	43
12	ETHICS AND DISSEMINATION .....	43
12.1	Research Ethics Approval & Local Governance Authorisation.....	43
12.2	Amendments to the protocol .....	43
12.3	Protocol Deviations and Serious Breaches .....	44
13	CONFIDENTIALITY .....	44
14	PARTICIPANT REIMBURSEMENT.....	44
15	FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST .....	44
16	DISSEMINATION AND TRANSLATION PLAN .....	44
17	ADDITIONAL CONSIDERATIONS.....	45
18	REFERENCES .....	46

19 APPENDICES .....	47
---------------------	----

## PROTOCOL SYNOPSIS

TITLE	A randomised controlled trial to assess the immunogenicity as well as safety and reactogenicity of standard dose versus fractional doses of COVID-19 vaccine (Pfizer-BioNTech) given as a booster dose after priming with Sinopharm, AstraZeneca or Sputnik in healthy adults in Mongolia.	
TRIAL DESCRIPTION	This clinical trial will be a single blind*, randomised study to determine the safety, reactogenicity and immunogenicity of booster doses of SARS-CoV-2 vaccines in adults. Both standard and fractional doses will be tested. * Subjects and assessors will be blinded to the vaccine dose for one week following administration, and laboratory staff will be blinded to vaccine dose associated with specimens.	
	Primary vaccine	Booster vaccines
	Sinopharm (BBIBP-CorV®)	1 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Standard dose (30µg) n= 200
		2 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Fractional dose (15µg) n= 200
	AstraZeneca (ChAdOx1-S, or Vaxzevria®)	3 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Standard dose (30µg) n= 100
		4 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Fractional dose (15µg) n= 100
	Sputnik V (Gam-COVID-Vac®)	3 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Standard dose (30µg) n= 100
		4 Pfizer-BioNTech (BNT162b2, or Comirnaty®) Fractional dose (15µg) n= 100
OBJECTIVES	<u>Primary objectives –</u> <ul style="list-style-type: none"> <li>To assess and compare the immune response measured as binding antibodies (IgG ELISA) following fractional versus standard doses of Pfizer vaccine given as single additional dose in adults 18 years and older in Mongolia who have been primed through previous vaccination with Astra Zeneca, Sinopharm or Sputnik vaccines. (Timepoint – 28 days post vaccination)</li> </ul>	

	<ul style="list-style-type: none"> <li>To assess the rate and severity of the reactogenicity within one-week post-booster for each schedule evaluated (Timepoint – daily, for seven days post vaccination)</li> </ul> <p><u>Secondary objectives</u> - (timepoint – 6 ,12, 18, and 24 months for all)</p> <ul style="list-style-type: none"> <li>To compare the duration of immunity, both humoral and cellular, over 24 months for fractional vs standard booster doses of the vaccines listed.</li> <li>To evaluate the different priming capacities of Sinopharm, AstraZeneca and Sputnik vaccines.</li> <li>To assess the impact of prior natural exposure on boosting regimens.</li> <li>To evaluate the safety of the booster dose regimens</li> </ul>
OUTCOMES AND OUTCOME MEASURES	<p>Outcomes</p> <ul style="list-style-type: none"> <li>Reactogenicity will be measured using the accepted standardised method for evaluation of systemic and local side effects following vaccination using a structured questionnaire for seven days post-vaccination. All moderate or severe reactions will be reviewed by study staff.</li> <li>All solicited adverse events (AE) will be collected for 7 days, all unsolicited AE will be collected for 28 days, and all medically attended AE will be collected to 3 months. SAE will be collected throughout the follow up period of 24 months. Adverse events of special interest will be categorised as per CEPI guidelines (1). Antibodies (binding and functional) and cellular immune responses will be measured (see outcome measures for details)</li> </ul> <p>Outcome measures</p> <p>Reactogenicity will be measured by recording the following parameters:</p> <ul style="list-style-type: none"> <li>Local reaction - pain, tenderness, erythema/redness, hardness, swelling, warmth, itch</li> <li>Systemic – Nausea, vomiting, diarrhoea, headache, fatigue/malaise, myalgia, arthralgia, fever, enlarged lymph nodes</li> </ul> <p>Immunology endpoints:</p> <p><i>Binding antibody</i> – These will be evaluated using the commercial Euroimmun S1 IgG ELISA on serum collected at 6 timepoints (baseline, 28 days, 6 months, 12 months, 18 months and 24 months. For all subjects, the 28 days post-vaccination sample will be assayed within four weeks of collection in Mongolia.</p>

	<p><i>Functional antibody</i> – All samples will be assayed using the GenScript cPass SARS-CoV-2 Neutralization Antibody detection kit, for both the ancestral Wuhan strain and Omicron variant RBD antigen.</p> <p><i>Neutralizing antibody</i> - A fraction of samples (20%) will be assessed using a SARS-CoV-2 neutralizing antibody assay undertaken at the Doherty Institute, Melbourne. Testing will be at 6 timepoints and for the Wuhan strain and 2 variants of concern.</p> <p><i>Cellular immunity</i> (on a 40% subset of samples at baseline, 28 days, 6 months, 12 months, 18 months and 24 months post-vaccination) as follows:–</p> <ul style="list-style-type: none"> <li>• <i>QuantiFERON Human IFN-γ SARS-CoV-2</i> (Qiagen) – These whole blood tests will be used on site.</li> <li>• Peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation within 12 hrs of collection and stored in liquid nitrogen at the lab in Ulaanbaatar, Mongolia prior to shipment to MCRI, Melbourne for testing. Cell mediated immunity assays will include IFN-γ Elispot, intracellular cytokine assays (flow cytometry) and multiplex cytokine assays.</li> </ul>
TRIAL POPULATION	Participants will be adults aged 18 years or older who have received two doses of either Sinopharm (BBIBP-CorV®), AstraZeneca (ChAdOx1-S, or Vaxzevria®), or Sputnik V (Gam-COVID-Vac®) ≥ 6 months before entering this study. There will be no upper age limit. 200 participants will be required in the Sinopharm groups and 100 per group in the Astra Zeneca and Sputnik arms, and therefore there will be 800 participants in total. Procedures will be implemented to ensure participants of all ages (aged 18 and above) are included and that there is an even age distribution (<50 and ≥50 years) in each group.
DESCRIPTION OF SITES ENROLLING PARTICIPANTS	Participants will be enrolled at government health centres or hospitals in Ulaanbaatar and provincial sites where Pfizer booster vaccinations are currently being offered to all adults.
DESCRIPTION OF INTERVENTIONS	The interventions being studied are as follows: Pfizer-BioNTech (BNT162b2, or Comirnaty®) Standard Dose (30µg) Pfizer-BioNTech (BNT162b2, or Comirnaty®) Fractional Dose (15µg)
TRIAL DURATION	The total duration of the trial will be 36 months. The initial recruitment period has been completed and took approximately 4 months. Each participant will have nine visits over a follow-up period of 24 months following their immunisation visit.



	To extend the follow-up from 12 months to 24 months after the study vaccine, participants will be invited to reconsent to the study extension following their 12 month visits.
PARTICIPANT DURATION	Participant duration will be 24 months, and there will be nine visits (six in-person visits and three phone calls). The DSMB will review participant safety regularly during the 24 months of participant involvement. Binding ELISA results (Euroimmun) will be reviewed by the DSMB for all participants who receive a fractional dose and compared with those who received a full dose. They will review all cases that do not meet the seroresponse definition (p38-39). The DSMB will decide if participants who received a fractional dose will be offered a further booster dose.

## GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
ANOVA	Analysis of Variance
AR	Adverse Reaction
ATAGI	Australian Technical Advisory Group on Immunisation
BRF	Biobank Registration Form (MCRI)
CEPI	Coalition for Epidemic Preparedness Innovations
CMI	Cell mediated immunity
CRF / eCRF	Case Report Form / electronic Case Report Form
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GMT	Geometric mean titres
HREC	Human Research Ethics Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IM	Intramuscular
MCRI	Murdoch Children's Research Institute
MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
PBMC	Peripheral blood mononuclear cells
PDI	Peter Doherty Research Institute
PI / CPI	Principal Investigator / Coordinating or Chief Principal Investigator
PI	Product Information (available for an approved drug or device)
QA	Quality Assurance
QC	Quality Control
RAT	Rapid Antigen Test
RGO	Research Governance Office
RCH	Royal Children's Hospital (Melbourne)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SoA	Schedule of Assessments
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SST	Serum separator tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

**INVESTIGATOR AGREEMENT**

I have read the protocol entitled “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.”.

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, and the good clinical practice guidelines adopted by the TGA [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments].

Changes to the protocol will only be implemented after written approval is received from the Human Research Ethics Committee, with the exception of medical emergencies.

I will ensure that trial staff fully understand and follow the protocol, and evidence of their training is documented on the trial training log.

Name	Role	Signature and date
Prof Kim Mulholland	Sponsor-investigator	
Dr Tsetsegsaikhan Batmunkh	Co-Principal Investigator	

## 1. ADMINISTRATIVE INFORMATION

### 1.1. Trial registration

#### 1.1.1. Trial registry

The trial will be registered on [ClinicalTrials.gov](https://clinicaltrials.gov) prior to trial commencement.

### 1.2. Sponsor

On behalf of the Sponsor, MCRI, the Sponsor-Investigator leading the trial, will undertake and oversee those Sponsor responsibilities delegated by the Sponsor. The delegated Sponsor responsibilities are documented in the study file.

<b>Trial Sponsor</b>	MCRI
<b>Contact name</b>	Fran Justice - <a href="mailto:fran.justice@mcri.edu.au">fran.justice@mcri.edu.au</a>
<b>Address</b>	Flemington Road, Parkville
<b>Sponsor-Investigator</b>	Prof Kim Mulholland

### 1.3. Expected duration of study

The expected duration of the study is 36 months which includes preparation and reporting. The recruitment period is anticipated to be 2 months and all participants will be followed up for 24 months. At or following the 12 month visit, participants will be invited to participate in a study extension and those who join will be followed until 24 months after their booster dose.

### 1.4. Contributorship

Name	Summary of contribution	Affiliation
Prof Kim Mulholland	Sponsor-investigator	MCRI
A/Prof Paul Licciardi	Investigator - Immunology	MCRI
Dr Claire von Mollendorf	Investigator – Medical/Epidemiology	MCRI
Dr Nadia Mazarakis	Investigator - Immunology	MCRI
Prof Nigel Crawford	Investigator - Advisor/ Chair of ATAGI/ Immunization specialist	MCRI
Prof Kanta Subbarao	Investigator - Immunology	PDI
A/Prof Siddhartha Mahanty	Investigator – Infectious Disease Specialist	PDI
Dr Lien Anh Ha Do	Investigator - Virology	MCRI
Dr Cattram Nguyen	Investigator - Statistics	MCRI
Dr Eleanor Neal	Investigator – Data Management/Analysis	MCRI
Dr John Hart	Investigator - Medical	MCRI
Ms Fran Justice	Investigator – Mongolia Project Manager	MCRI
Dr Kerryn Moore	Investigator - Statistician	MCRI

Name	Summary of contribution	Affiliation
Dr Tsetsegsaikhan Batmunkh	Principal Investigator (Mongolia)	MoH, Mongolia
Dr Unursaikhan Surenjav	Investigator	Public Health Centre, Mongolia
Dr Khishigjargal Batsukh	Investigator – Study Physician	State First Hospital, Mongolia
Dr Batbayar Ochirbat	Investigator	MoH, Mongolia
Dr Bilegtsaikhan Tsolmon	Investigator	NCCD, Mongolia
Dr. Dashpagam Otgonbayar	Investigator	NCCD, Mongolia
Dr Chinbayar Tserendorj	Investigator	NCCD, Mongolia
Dr Azjargal Enkhsaikhan	Investigator	MMRA, Mongolia
Dr Narantuya Namjil	Laboratory consultant	Onoshmed Laboratory, Mongolia
Dr Otgonbold Jamyandorj	Investigator	City Health Department, Mongolia
Dr Sarantsetseg Jamyan	Laboratory consultant	State First Hospital, Mongolia
Dr Tsegmed Sambuu	Data manager	Public Health Centre, Mongolia
Dr Gantuya Dorj	Data manager	National Medical Science University
Dr Otgonjargal Amraa	Investigator – Study Physician	NCCD, Mongolia
Ms Khaliunaa Mashbaatar	Investigator - Laboratory	NCCD, Mongolia

### 1.5. Stakeholder involvement

The Coalition for Epidemic Preparedness Innovations (CEPI) is a foundation that takes donations from public, private, philanthropic, and civil society organisations to finance independent research projects to develop vaccines against emerging infectious diseases. CEPI is providing funding for this study. CEPI has reviewed this protocol, and they have been involved in the development of the project.

## 2. INTRODUCTION AND BACKGROUND

### 2.1. Trial rationale and aim

Additional or booster doses of Covid-19 vaccines are now used in most countries although data remain insufficient regarding optimal timing, target groups, duration of protection and safety. Although vaccine distribution is now generally sufficient, there remain a number of critical outstanding questions related to the use of booster doses. These include optimal timing, particularly after priming with inactivated vaccines that provide shorter duration of protection, and the potential use of fractional dosage. We have chosen three sites (Australia, Mongolia, and Indonesia) which together will be suitable to answer these questions.

Due to the rapidly developing field much of the data had been presented in various WHO meetings, but is currently unpublished (Appendix 1). Currently the most comprehensive published booster study

is the UK-based multi-site CovBoost study (2). This study demonstrated the use of fractional doses of Pfizer vaccine to be very close to equivalent in patients primed with AstraZeneca or Pfizer vaccines. The CovBoost study did not include patients primed with inactivated vaccines. This protocol covers the component to be studied in Mongolia and will focus on booster regimens relevant to Mongolia and not previously studied elsewhere in the world.

## **2.2. Background**

It is clear that all Covid-19 vaccines are not equal. While all the EUL listed products are effective in the short term for preventing severe and fatal Covid-19, prevention of mild or asymptomatic infection is variable, and the duration of protection seems limited and highly variable. When this study commenced, many low- or middle-income countries were unable to access sufficient Covid-19 vaccines for their population. However, other countries were already providing booster doses and it was clear that more evidence on boosting immunity was required. Our understanding of boosting immunity with different vaccines, particularly following priming with the inactivated vaccines, CoronaVac and BBIBP-CorV, remains unclear. We are proceeding with this project for the following reasons:

1. Some countries that have achieved high coverage with inactivated vaccines with little impact on overall disease rates have begun programs of heterologous (e.g., UAE, Mongolia) or homologous (e.g., Chile) boosting, without a strong scientific basis for the schedules chosen. Guidance is needed on how to design optimal booster vaccine strategies.
2. Countries that began vaccination early with support from COVAX have usually started by vaccinating front line health workers (e.g., Indonesia). With minimal vaccination of the general population, health workers have been exposed to large numbers of infected patients and increasing numbers of Covid-19 illness and death among health care workers have led to informal attempts to boost immunity for this group (3).
3. The use of fractional doses as boosters has been shown to produce similar boosting to standard doses for two vaccines (Johnson & Johnson (4) and Moderna (5)), and an unpublished study from Thailand (Appendix 1) and data from UK (2) have shown a similar effect with half dose Pfizer vaccine. The use of fractional doses for booster doses and potentially primary series could save large volumes of vaccine, potentially freeing up vaccine for communities that currently lack access. Updated guidelines in the US and UK recommend the use of half dose (50µg) for Moderna booster doses, while follow-up of earlier studies indicate that a 20µg dose is likely to be adequate as a booster (6, 7).

Vaccine breakthrough infections are made more likely due to host immune factors such as waning immunity (e.g. due to low neutralising antibodies) as well as virological factors, particularly new variants such as Omicron that evade the immune response. The role that different factors play in breakthrough infections and the immune boosting of natural infections against SARS-CoV-2 for different variants is still being defined.

### 2.3. Study follow-up rationale

The World Health Organization's Strategic Advisory Group of Experts on Immunization (WHO SAGE) revised the roadmap for prioritizing the use of COVID-19 vaccines in March 2023. The new roadmap accounted for the Omicron impact and high population-level immunity due to infection and vaccination. The roadmap outlined three priority groups for COVID-19 vaccination based on risk of severe disease and death. SAGE recommended an additional booster 6-12 months (e.g second or third booster) after the last dose for the high priority group (older adults, younger adults with significant comorbidities, people with immunocompromising conditions, pregnant women and frontline health workers). SAGE did not routinely recommend boosters for the medium or low risk groups. Extending surveillance to investigate the immunogenicity of these groups at additional timepoints would provide longitudinal data to support the need for boosters in different risk groups, and document breakthrough infections and will help to advise the next steps for an appropriate COVID-19 vaccine schedule.

### 2.4. Risk/Benefit assessment

#### 2.4.1. Known potential risks

This study will provide safety data of the booster regimens being studied and will collect safety data for fractional doses of the booster vaccines.

The safety profiles of the vaccine being tested are well described (see Appendix 2 - Product information sheets).

#### Possible lower efficacy of fractional booster dose

Participants who receive a fractional dose are at a small risk of not receiving sufficient vaccine to protect against COVID-19.

#### Risks associated with sample taking

Participants may experience discomfort and/or localised bruising from venepuncture and there is a small risk of fainting. The total volume of blood drawn over a 24-month period will be up to 180mls which is safe in otherwise healthy adults.

#### Allergic reactions

Allergic reactions may occur to any of the constituents of the booster vaccine. These may range from mild to severe but are usually rare. Patients should be questioned regarding allergic reactions to any vaccines in the past. All participants will have previously received two doses of a Covid-19 vaccine.

#### Reactogenicity

Although it is anticipated that participants might experience more reactogenicity if their booster vaccine differs from the vaccine used in their primary two dose schedule, a recent study showed similar reactogenicity between homologous and heterologous booster schedules. Those who received fractional doses may also be expected to have lower reactogenicity. Superior immunogenicity has been reported with heterologous boosting schedules.

## **2.4.2. Assessment of potential risks and benefits**

The vaccine being used in this study is a registered product available to the general population for booster vaccination. The trial component is to examine administration of fractional doses. The risk of fractional doses is the potential for lower effectiveness, while the use of heterologous boosters poses the risks of increased reactogenicity and uncertain effectiveness. These factors are balanced against the potential benefits of heterologous boosting which include preservation of vaccine through the use of fractional doses, and potentially superior immunogenicity, and broader protection. It should be noted that the risks and benefits from homologous boosting also remain unclear.

### **2.4.1. Known potential benefits**

Booster doses of Covid-19 vaccines are available to all adults in Mongolia and there may be no direct benefits for participants enrolling in this study, apart from the opportunity to learn their antibody response following the booster. In addition, the fractional dose booster may be shown to be equally effective with less reactogenicity. Participants will receive a heterologous boost which may be shown to be superior to a homologous boost. Studies have shown that mRNA boosting potentially offers superior immunogenicity for individuals primed with AstraZeneca.

While early reports from Israel and the US confirm the effectiveness of a first booster dose of Covid-19 vaccine in some heterologous or homologous regimens, there is only limited data on the use of fractional dosage in heterologous regimens. This study will provide data crucial to designing optimal vaccine strategies in Mongolia and other countries that have used Sinopharm (*BBIBP-CorV*®), AstraZeneca (ChAdOx1-S, or *Vaxzevria*®) or Sputnik V (Gam-COVID-Vac) as primary two dose regimens.

## **3. TRIAL OBJECTIVES AND OUTCOMES**

### **3.1 Objectives**

#### **3.1.1 Primary objectives**

- To 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)
- To assess the rate and severity of reactogenicity within one-week post-booster for each schedule evaluated.

#### **3.1.2 Secondary objectives**

The secondary objectives are to:

- To compare the immunogenicity, both humoral and cellular, over 24 months following fractional and standard booster doses of the vaccines listed.



- To evaluate the different priming capacities of Sinopharm, AstraZeneca and Sputnik vaccines
- To assess the impact of prior natural exposure on boosting regimens.
- To evaluate the safety of the booster dose regimens

## 3.2 Outcomes

### 3.2.1 Primary outcomes

#### Immune response

*Binding antibody* – These will be evaluated using the commercial Euroimmun S1 IgG ELISA on all serum samples collected at 6 timepoints (baseline, 28 days, 6 months, 12 months, 18 months and 24 months). Assays for all subjects will be completed within 4 weeks of sample collection. Assays on the 28 days post-vaccination sample, comparing fractional and standard dose, will be reviewed by the DSMB.

#### Reactogenicity

Reactogenicity will be measured using the accepted standardised method to evaluate systemic and local side effects following vaccination using a structured questionnaire for days post-vaccination as outlined in Table 1 below.

Table 1. Grading system for evaluation of systemic and local side effects following vaccination (8).

<i>Local Reaction to Injectable Product<sup>a</sup></i>				
	<i>Mild (Grade 1)</i>	<i>Moderate (Grade 2)</i>	<i>Severe (Grade 3)</i>	<i>Potentially Life Threatening (Grade 4)</i>
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness <sup>b</sup>	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling <sup>c</sup>	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Hardness <sup>c</sup>	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Axillary lymphadenopathy	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Warmth (usually reported with redness)	Absence		Presence	
Itch	Absence		Presence	
<sup>a</sup> For all parameters, grade 0 will be recorded if specific symptoms are absent.				
<sup>b</sup> The measurement should be recorded as a continuous variable in addition to grading the measured local reaction at the greatest single diameter.				
<sup>c</sup> Hardness and swelling should be evaluated and graded using the functional scale as well as the actual measurement.				
<i>Systemic (General)<sup>a</sup></i>				

	<i>Mild (Grade 1)</i>	<i>Moderate (Grade 2)</i>	<i>Severe (Grade 3)</i>	<i>Potentially Life Threatening (Grade 4)</i>
Fever (°C) Oral or axillary temperature	38.0 – 38.4	38.5 – 38.9	39.0 – 40	>40
Nausea	No interference with activity	Some interference with activity	Prevents daily activity	ER visit or hospitalization
Vomiting	No interference with activity or 1 – 2 episodes /24 hours	Some interference with activity or >2 episodes/24 h ours	Prevents daily activity, or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhoea	No interference with activity	Some interference with activity	Prevents daily activity, or requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Headache	No interference with activity	Repeated use of nonnarcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/Malaise	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia (muscle pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Arthralgia (joint pain)	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
<sup>a</sup> For all parameters, grade 0 will be recorded if specific symptoms are absent or temperature is <38.0. In addition, appearance of the following potential signs of myocarditis/pericarditis will prompt referral for cardiology evaluation: Chest pain, dyspnoea, painful breathing, palpitations, or syncope.				

### 3.2.2 Secondary outcomes

#### Immunogenicity

*Functional antibody* – All samples at all timepoints will be assayed using the GenScript cPass

SARS-CoV-2 Neutralization Antibody detection kit for both the Wuhan strain and Omicron variant RBD antigen in Mongolia.

*Neutralizing antibody* - A fraction of samples (20%) will be assessed using a SARS-CoV-2 microneutralisation assay undertaken at the PDI, Melbourne. Assays will be done at all six timepoints to the Wuhan strain (first generation COVID vaccine) and for 2 Variants of Concern.

*Cellular immunity* - Cellular immunity will be assessed on a subset of 40% of participants, with samples collected at six timepoints: baseline, 28 days, 6 months, 12 months, 18 months and 24 months post-vaccination as follows:

- *QuantiFERON Human IFN- $\gamma$  SARS-CoV-2* (Qiagen) will be performed using heparinised whole blood
- Peripheral blood mononuclear cells (PBMCs) will also be isolated by density gradient centrifugation within 12 hours of collection and stored in liquid nitrogen at MCRI. Assays performed will include IFN- $\gamma$  Elispot, intracellular cytokine assays (flow cytometry) and multiplex cytokine assays.
- To assess the impact of prior natural exposure on boosting regimens by comparing antibody responses between those who do/don't report a previous COVID infection.

#### Safety

- All solicited adverse events (AE) will be collected for 7 days, all unsolicited AE will be collected for 28 days, and all medically attended AE will be collected for 3 months. SAE will be collected throughout the follow up period of 24 months.

## 4 TRIAL DESIGN

### 4.1 Overall design

This clinical trial will be a single blind, randomised study to determine the immunogenicity and reactogenicity of booster doses of SARS-CoV-2 vaccines in adults. Both fractional and standard doses will be tested.

The groups are described below. The trial intervention will be a single booster dose of vaccine: -

Primary vaccine	Booster vaccines
Sinopharm ( <i>BBIBP-CorV</i> <sup>®</sup> )	1. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Standard dose (30 $\mu$ g) n= 200
	2. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Fractional dose (15 $\mu$ g) n= 200
AstraZeneca (ChAdOx1-S, or <i>Vaxzevria</i> <sup>®</sup> )	3. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Standard dose (30 $\mu$ g) n= 100
	4. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Fractional dose (15 $\mu$ g) n= 100
Sputnik V (Gam-COVID-Vac <sup>®</sup> )	5. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Standard dose (30 $\mu$ g) n= 100
	6. Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> <sup>®</sup> ) Fractional dose (15 $\mu$ g) n= 100

The trial intervention will be given 6 or more months after the primary vaccine schedule. The groups size will be either 200 (Sinopharm groups) or 100 (AstraZeneca and Sputnik groups) individuals with an even spread of participants above and below 50 years in each group. The Sinopharm vaccinee impact is of greater importance to Mongolia as this is the main vaccine used for the primary series in Mongolia. In addition, Sinopharm is the least effective of the 3 vaccines used, so we expect to see evidence of more breakthrough cases and therefore a wider range of pre-booster immunity levels. The trial will be conducted at multiple sites (health centres, hospital or vaccination clinics) in Ulaanbaatar and provincial sites.

The trial will be single blind. The participants and those evaluating reactogenicity will be blinded to the vaccine dose allocation for the first 28 days following vaccination. After that, both the clinical investigators and potentially participants will be aware of their investigational product dose allocation. Immunologists and laboratory staff will remain blinded to the investigational product dose allocation.

#### **4.2 Justification for dose**

This project is designed to evaluate the potential use of fractional dose and heterologous booster regimens for individuals who have previously received two doses of Covid-19 vaccine. The fractional dose has advantages for the individual and the broad community. At an individual level, the likelihood of moderate adverse reactions is reduced by the use of a fractional dose. Existing data suggests that immunogenicity and effectiveness will be maintained, but this will be evaluated early in the project and if immunogenicity proves to be inadequate this will be addressed according to the recommendations of the DSMB. At a national and global level, the approach carries the potential to greatly expand the availability of Covid-19 vaccine, helping to correct the inequity that currently characterises the global Covid-19 situation.

#### **4.3 Trial population**

The trial population will be adults 18 years and older who have received two doses of Covid-19 vaccines, either Sinopharm (*BBIBP-CorV*®) AstraZeneca (*ChAdOx1-S*, *Vaxzevria*®) or Sputnik V (*Gam-COVID-Vac*®) at least 6 months prior. There will be no upper age limit.

Procedures will be implemented to ensure participants of all ages (aged 18 and above) are included and that there is an even age distribution (<50 and ≥50 years) in each group.

#### **4.4 Eligibility criteria**

If informed consent is granted, study staff will ensure that all the eligibility criteria are met. Potential participants must meet all the inclusion criteria and none of the exclusion criteria to be eligible.

##### **4.4.1 Inclusion criteria**

**Each participant must meet all the following criteria to be enrolled in this trial:**

1. Have completed two doses of Sinopharm, AstraZeneca or Sputnik vaccines with the recommended schedule at least 6 months prior to the date of enrolment
2. Willing and able to give written informed consent
3. Aged 18 years or above

4. Willing to complete the follow-up requirements of the study

Note that subjects with comorbidities other than those listed below as contraindications will be included. Pregnant women or women who may become pregnant will be included.

#### **4.4.2 Exclusion criteria**

**Potential participant meeting any of the criteria below will be excluded from this trial:**

1. Received 3 doses of COVID-19 vaccine
2. Received 2 doses of COVID-19 less than 6 months prior to the start of the trial
3. Currently on immunosuppressive medication or anti-cancer chemotherapy
4. Known HIV infection
5. Congenital immune deficiency syndrome
6. Has received immunoglobulin or other blood products in the 3 months prior to vaccination
7. Study staff and their relatives
8. Have a history of a severe allergic reaction to any COVID-19 vaccines or have a medical exception to receiving further COVID-19 vaccines

Symptomatic potential participants (cough, sore throat, fever or other symptoms) or those who have tested positive (on PCR or RAT) or are waiting for a SARS-CoV-2 test result will not be enrolled. Such potential participants will be asked to return once their symptoms have resolved and their SARS-CoV-2 test is negative if they were tested.

#### **4.5 Lifestyle considerations**

Not Applicable.

#### **4.6 Screen failures**

Screen failures are defined as participants who consent to participate in the trial but are found during screening procedures to be ineligible. They, therefore, do not receive the intervention and are not randomised. We anticipate that there will be very few screen failures due to the minimal inclusion/exclusion criteria.

#### **4.7 Recruitment and identification of potential participants**

The study will be offered to attendees at District Health centres and hospitals to those who previously attended the clinics for their priming vaccinations. Those interested will be provided with the participant information sheet and consent form (PICF) 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 will be recorded on a recruitment log. If the potential participant decides not to participate no identifying information will be retained.

## 4.8 Consent

Informed consent is a process that is initiated prior to the agreement to participate in the trial and continues throughout study participation. Discussion of risks and possible benefits of this vaccination will be provided to the potential participants prior to obtaining informed consent. Trial staff will go through the Informed Consent Form (ICF), which describes in plain language the trial interventions, the study procedures, and the risks and benefits of participation. The ICF will be HREC-approved and the potential participant will be asked to read and review the ICF. The trial staff will then explain the research study further and answer any questions that may arise.

Written documentation of informed consent is required prior to enrolment into the trial. The potential participant will sign and date the final page of the ICF. The trial staff will witness the consent, confirming that the trial has been fully explained and that the participant understands the rationale for the trial and the trial processes. The potential participant will be informed that they are free to withdraw from the trial at any time. A copy of the ICF will be given to the potential participant.

Following or at the 12 month visit, participants will be invited to participate in an extension study with follow-up visits at 18 months and 24 months. They will be asked to sign a new consent form for the extension.

## 5 INTERVENTION

### 5.1 Treatment arms

Treatment Arms	Route	Dose
1) Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> ®)	IM	Standard Dose - (30µg)
2) Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> ®)	IM	Fractional Dose - (15µg)

### 5.2 Trial Intervention(s)

Pfizer BioNTech (BNT162b2) BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. BNT162b2 encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA is then degraded within days. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection.

#### 5.2.1 Description of trial investigational products

##### 5.2.1.1 Trial Products

#### Active substance

The Pfizer-BioNTech COVID-19 vaccine, BNT162b2, encodes a P2 mutant spike protein and is formulated as an RNA-lipid nanoparticle (LNP) of nucleoside-modified mRNA (modRNA).

<b>Trade or Generic name</b>	Pfizer-BioNTech (BNT162b2, or <i>Comirnaty</i> ®)
<b>Dosage form</b>	Liquid for injection – standard dose is 0.3ml containing 30µg; fractional dose is 0.15ml containing 15ug.
<b>Route of administration</b>	Intramuscular injection

### 5.2.2 Dosage

The standard dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine and is currently the standard dose that is used for a booster. A half dose is 15 µg contained in 0.15ml of the diluted vaccine. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 5 standard doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules.

### 5.2.3 Dose modification

Dose modification is not permitted and must be given as per randomisation.

### 5.2.4 Storage, preparation, dispensing and administration of trial drug

All study vaccines will be stored at the central vaccine storage building at the National Center for Communicable Diseases (NCCD) and will be stored in accordance with the manufacturers' recommendations. See below:

- The Pfizer BioNTech vaccine should be stored at -70°C +/- 10°C and has shelf life of 6 months. Once thawed, the vaccine may be stored for 31 days at 2-8°C.

Vaccine accountability, storage, shipment, and handling will be in accordance with relevant SOPs and forms.

### 5.2.5 Product accountability

The trial vaccines will be provided by the Ministry of Health at District Health centres and hospitals. Study nurses will collect supplies each day and return any unused vaccines at the end of the day. The study nurses will ensure that storage requirements are maintained. Study vaccines will be administered by unblinded vaccinators, who will maintain blinding such that those evaluating reactogenicity are kept blinded during the first week post-vaccination.

The unblinded vaccinators will keep accurate records regarding when and how much trial vaccine is dispensed and used for each participant in the trial. Reasons for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of trial vaccine received, dispensed, consumed, and returned. Any discrepancies will be investigated, resolved, and documented by the trial team. Unused trial vaccines will be destroyed in compliance with applicable regulations.

Detailed information regarding product accountability will be provided in an SOP.



### 5.2.6 Excluded medications and treatments

There are no excluded medications or treatments apart from those associated with exclusions listed in section 4.4.2.

### 5.2.7 Concomitant therapy

Concomitant medications taken by participants during the study will be documented, as outlined below, as part of the safety review procedures.

From the study start until 24 months, only the following medications of interest will be recorded:

- Any vaccine.
- Any investigational products.
- Immunosuppressive therapies.
- Therapies taken for suspected or confirmed COVID-19

Concomitant medications records will include the drug name, total daily dose, route of administration, start and stop date of administration, and indication for use.

### 5.2.8 Discontinuation from trial intervention

See Section 7.2.8.

## 6 RANDOMISATION AND BLINDING

Once consent has been obtained, and following eligibility assessment, eligible participants will be recruited and randomised. Participants will be randomised 1:1 to one of the 2 intervention groups (*Comirnaty*<sup>®</sup> standard dose, *Comirnaty*<sup>®</sup> fractional dose) stratified by the primary vaccine received (*BBIBP-CorV*<sup>®</sup>, *Comirnaty*<sup>®</sup> or *Gam-COVID-Vac*<sup>®</sup>) and age (<50 and ≥50 years). A secure, password-protected web-based randomisation schedule will be provided by an independent statistician from the Melbourne Children's Trial Centre at the Murdoch Children's Research Institute. Blocked randomisation will be used with random blocks of permuted length. To ensure there are even numbers by primary vaccine and age group, participants will be recruited until the number required in each stratum has been reached.

40% of participants from each group will be included in the CMI subgroup analysis. The strata that will be used for CMI analysis will be identified at this time, and measures will be taken to ensure that the age strata (<50 and ≥50 years) are equally represented in this group with a separate randomisation list. Only 10-20 CMI samples can be processed per day. We will therefore recruit the first 10-20 participants to participate in this sub study per day. Daily recruitment for the sub study will be stopped once the maximum number is reached.

### 6.1 Concealment mechanism

Randomisation will be stratified according to age (<50 and ≥50 years) and primary vaccine (*BBIBP-CorV*<sup>®</sup> or *Comirnaty*<sup>®</sup>). Using REDCap the participants will be randomised to one of two groups in a 1:1 dose allocation ratio. (see table below).

Primary vaccines	Age	Booster vaccine	Dose given
Sinopharm, AstraZeneca, or Sputnik V	<50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg
	≥50	Pfizer-BioNTech	30µg
		Pfizer-BioNTech	15µg

Study staff (unblinded vaccinator) involved in administering the vaccine will use REDCap to receive the information on the participant's randomisation number and vaccine dose so they will be aware of which vaccine the participant is receiving. The participants themselves will remain blinded to their vaccine dose (until day 28 post vaccination). Study staff involved in assessing reactogenicity will be blinded to each participant's vaccine dose until 28 days post vaccination, as this variable will be hidden in REDCap for blinded study staff. Study staff involved in assessing immunogenicity outcomes will remain blinded during the analysis of specimens.

Vaccines will be prepared out of sight of the participant and the blind will be maintained by applying masking tape over the vaccine syringe, so the study participant can't see the volume.

Only the study nurse (unblinded vaccinator) administering the vaccine will be aware of which vaccine is given to the study participant.

## 6.2 Breaking of the trial blind

### 6.2.1 On trial

The study will be blinded for the first 28 days only. In the unlikely event that it becomes necessary to unblind during this period that decision will be taken by the PI, and the subject and physicians who may be caring for the subject will be made aware of the dose allocation.

## 7 TRIAL VISITS AND PROCEDURES

### 7.1 Schedule of assessments

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Location	At health centre	Phone call	Phone call	At health centre	Phone call	At health centre	At health centre	At health centre	At health centre
Timing	Day 0	Day 1	Day 7	Day 28	3 months	6 months	12 months	18 months	24 months
Visit window			+ 3 days	+ 7 days	+/- 14 days	+/- 14 days	+/- 30 days	+/- 30 days	+/- 30 days

Informed consent	X								
Eligibility confirmation	X								
Randomisation	X								
Blood sampling	X			X		X	X	X	X
Vaccination	X								
Vital signs	X								
Issue diary card, ruler and thermometer	X								
Collect diary card	X (daily)								
Documentation of Solicited AE	X	X	X						
Documentation of unsolicited AE	X	X	X	X					
Documentation of medically attended AE	X	X	X	X	X				
Documentation of SAE	Throughout study period								
Documentation of confirmed breakthrough COVID-19 infection	Throughout study period								

## **7.2 Description of procedures**

### **7.2.1 Visit 1 (Day 0)**

Informed consent must be signed by both participant and study doctor or nurse.

Participant eligibility must be confirmed prior to randomisation and on the same date as administration of the investigational product.

Eligibility must be confirmed by a study doctor or study nurse. Randomisation must be completed by the unblinded vaccinator who will document the participant's randomisation number on the enrolment log.

Study staff will administer a Visit 1 questionnaire documenting demographic information, height and weight, dates and type of primary COVID-19 vaccine, prior confirmed SARs-Cov-2 infection(s) documented in medical records, any comorbidities and concomitant medication.

The following vital signs will be recorded by a study doctor or study nurse prior to vaccination: temperature, pulse rate, respiratory rate, and blood pressure.

Prior to vaccination, for all participants, 5mL of blood will be collected and processed according to the SOP. CMI participants will have an additional 25ml collected and processed for Quantiferon analysis and PBMC separation and storage.

Following randomisation, the unblinded vaccinator will administer the applicable vaccine to the participant.

Study staff will provide the participant with a hard copy reactogenicity diary card or email them a REDCap survey form. Study staff will instruct the participant on how to complete the diary card for the day of vaccination and seven days following vaccination. Patients who complete a hard copy diary card will be asked to bring it to their day 28 visit so that the information can be entered in the REDCap database.

Study staff will provide the participant with a thermometer and ruler and detailed instructions on how to use these for measuring temperature and potential erythema and induration. Study staff will provide the participant with a schedule of visit appointments and instruct the participant on how to contact the study staff in case of any SAE or symptoms suggestive of COVID-19.

Study staff will keep the participant under observation for minimum 15 minutes and document any immediate adverse events.

### **7.2.1 Visit 2 (Day 1)**

Study staff will contact the participant by phone approximately 24 hours after vaccination to review and document adverse events.

### **7.2.2 Visit 3 (Day 7)**

Study staff will contact the participant by phone one week after vaccination. If participants have a hard copy card study staff will ask participants to read the details over the phone or send a picture of their hard copy diary card (with the name obscured) for review. If the participant completed the REDCap

diary card, study staff will review it with them to confirm that all symptoms are captured. Study staff will also document any significant, unexpected, serious or unusual adverse events on the AE CRF.

#### **7.2.3 Visit 4 (Day 28)**

An in-person visit will be conducted 28 days following vaccination. Participants with hard copy diary cards will be asked to bring the card to this visit for collection. All Unsolicited Adverse Events will be documented. Study staff will also document any new information regarding solicited adverse events with onset up to 7 days following vaccination, such as resolution. The participant will be informed which vaccine dosage they received based on entry into the CRF by the unblinded staff member.

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 5mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. SST tubes should be kept cold (around 4 degrees) if not transferred within 3 hours.

#### **7.2.4 Visit 5 (3 Months)**

Study staff will contact the participant by phone and document information on any medically attended AE or SAE.

Study staff will also document any new information regarding unsolicited adverse events with onset up to 28 days following vaccination, such as resolution.

#### **7.2.5 Visit 6 (6 Months)**

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 5mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. SST tubes should be kept cold (around 4 degrees) if not transferred within 3 hours. An SMS will be sent to participants monthly between Visit 6 and Visit 7 to check for any breakthrough infections and AE/SAEs.

#### **7.2.6 Visit 7 (12 Months)**

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 5mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. SST tubes should be kept cold (around 4 degrees) if not transferred within 3 hours. Participants will be invited to participate for a further 12 months and will be re-consented for Visit 8 and 9. (For those participants who have already attended their 12 month visit, a phone call will be made and consent signed at Visit 8). All participants will receive a gift card for 50,000 Mongolian Tugrik (~14 USD) at 12 months as some visits will be completed at time of extension. An SMS will be sent to participants monthly between Visit 7 and Visit 8 to check for any breakthrough infections and SAEs.

### **7.2.7 Visit 8 (18 Months)**

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 5mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. SST tubes should be kept cold (around 4 degrees) if not transferred within 3 hours. An SMS will be sent to participants monthly between Visit 8 and Visit 9 to check for any breakthrough infections and SAEs. Participants will be asked if they have received another covid vaccine since their last visit.

### **7.2.8 Visit 9 (24 Months)**

For all participants, 5mL of blood will be collected in an SST tube. For participants in the CMI subset, 5mL of blood for Quantiferon test will be collected in a heparinised tube, and 20mL of blood for PBMC will be collected in a heparinised tube. Blood samples will be kept at room temperature and transferred to the laboratory within 3 hours of collection. SST tubes should be kept cold (around 4 degrees) if not transferred within 3 hours.

Participants who complete the 24-month study period will receive a gift card for 50,000 Mongolian Tugrik (~14 USD). If they request, results of their tests will be shared and discussed with them by a member of the study team at any visit if available. Participants will be asked if they have received another Covid-19 vaccine since their last visit.

### **7.2.9 Unscheduled visits**

If any participant develops symptoms of Covid-19 or tests positive on a rapid antigen test (RAT), they will be instructed to contact the Study Team and to get a PCR test at the nearest facility. If the test (RAT or PCR) is positive the Study Team will seek to obtain a specimen for virology, either residual from the specimen that tested positive, or an additional swab once the positive result is known. One month after the positive test a 5ml blood sample will be collected and serum stored for future serological analysis if the participant consents. Participants will be reimbursed for unscheduled visits. The participant will otherwise continue with scheduled study visits. The virology sample will be tested at the National Centre for Communicable Diseases in Mongolia. If there are a large number of breakthrough infections, all severe cases and a proportion of mild cases will be prioritised for sequencing. The study team will maintain telephone contact daily with the participant for the course of his/her illness and fully document all telephone calls. With the subject's permission the Team will seek clinical data from the health care providers or hospital in the event that the subject becomes clinically ill. If breakthrough infections are not being captured using RAT or PCR testing, an additional detection method to measure IgG antibodies specific for SARS-CoV-2 nucleocapsid (N) protein in serum (in-house ELISA) may be used to identify if an infection has occurred. Any confirmed breakthrough infections will be documented until the end of the study (Visit 9- 24 months).

### **7.2.10 Withdrawal of consent - participant withdraws from all trial participation**

A participant has the right to withdraw from the trial at any time and for any reason and is not obliged to give his or her reasons for doing so. The Investigator may withdraw the participant at any time in the

interests of the participants' health and well-being. In addition, the participant may withdraw/be withdrawn for any of the following reasons:

- Administrative decision by the Investigator
- Ineligibility (either arising during the trial or retrospectively, having been overlooked at screening).
- Significant protocol deviation
- Participant non-compliance with study requirements

The reason for withdrawal will be recorded in the CRF. If the participant has an AE at the time of withdrawal, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilised or a non-trial related causality has been assigned.

If a participant withdraws from the study, storage of samples and data collected before their withdrawal will still be used in the analysis, unless the participant specifically requests otherwise.

#### **7.2.11 Losses to follow-up**

A participant will be considered lost to follow-up if he/she fails to return for two consecutive visits and is unable to be contacted by the trial staff. The following action must be taken if a participant fails to return to the clinic for a required trial visit:

- Trial staff will attempt to contact the participant within one week of the missed visit and reschedule the visit.
- Before a participant is deemed lost to follow-up, trial staff will make every effort to regain contact. Three telephone calls will be made, and two emails sent. All contact attempts will be documented in the participants CRF
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the trial with a primary reason of lost to follow-up.

#### **7.2.12 Replacements**

Participants who have been randomised and enrolled may NOT be replaced.

#### **7.2.13 Trial Closure**

The end of the trial is the date of the last assay conducted on the last sample collected.

### **8 SAFETY MONITORING AND REPORTING**

#### **8.1.1 Definitions for use in trials involving investigational medicinal products**

##### **Participant-specific adverse events**

Adverse events must be assessed to determine each of the following:

1. Seriousness
2. Relatedness (i.e., causal relationship)
3. Expectedness

Adverse Event (AE): Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and does not necessarily have a causal relationship with this treatment.

Adverse Reaction (AR): Any untoward and unintended response to an investigational medicinal product related to any dose administered.

*Comment: All adverse events judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to an investigational medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.*

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR): Any adverse event/adverse reaction that results in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is a congenital anomaly or birth defect.

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe. Medical and scientific judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. **Important medical events** that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

#### **Safety issues (requiring expedited reporting)**

The following definitions describe additional safety events that require expedited reporting to stakeholders including the Sponsor, Investigators, HREC, local governance office and TGA:

Significant Safety Issue (SSI): A safety issue that could adversely affect the safety of participants or materially impact the continued ethical acceptability or conduct of the trial.

Comment: An SSI is a new safety issue or validated signal considered by the Sponsor in relation to the investigational medicinal product that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the investigational medicinal product, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the investigational medicinal product.

Urgent Safety Measure (USM): A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of SSI that can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

## **8.2 Capturing and eliciting adverse event/reaction information**

Participants will be asked to record local and systemic AEs for 7 days (and longer if symptoms persist at day seven, until resolution or stabilisation) following vaccination in the electronic or paper diary card (solicited AEs). Unsolicited AEs All local and systemic AEs occurring in the 28 days following vaccination



observed by the Investigator or reported by the participant, whether or not attributed to study medication, will also be recorded in participant diary and CRF.

Serious adverse events (SAE's) will be followed up for the duration of the trial. Adverse events of special interest will be categorised as per CEPI guidelines (1).

### 8.3 Documentation of AEs

The AE will be described in the source documents (e.g., electronic or paper diary card) and captured on the CRF and will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity (mild, moderate, or severe– what is the impact on the participant's daily life?)
- Seriousness (i.e., is it an SAE?)
- Any action taken, (e.g., treatment, follow-up tests)
- The outcome (recovery, death, continuing, worsening)
- The likelihood of the relationship of the AE to the trial treatment (Unrelated, Possible, Probable, Definite)

Changes in the severity of an AE will be reported. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

### 8.4 Assessing the relatedness (causality) of a participant's AE

The relationship of the event to the trial intervention will be graded/ assessed as follows:

<b>Unrelated</b>	Unlikely temporal relationship to study product and Alternate aetiology likely (clinical state, environmental or other interventions) and does not follow known typical or plausible pattern of response to study product
<b>Possible</b>	Reasonable temporal relationship to study product; or event not readily produced by clinical state, environmental or other interventions; or similar pattern of response to that seen with other vaccines
<b>Probable</b>	Reasonable temporal relationship to study product; and event not readily produced by clinical state, environment, or other interventions or known pattern of response seen with other vaccines
<b>Definite</b>	Reasonable temporal relationship to study product; and event not readily produced by clinical state, environment, or other interventions; and known pattern of response seen with other vaccines

### 8.5 Assessing the severity of a participant's AE

The severity of an Adverse Events will be graded/ assessed as follows:

<b>Grade 0</b>	None
----------------	------

<b>Grade 1</b>	Mild: Transient or mild discomfort (< 48 hours); No interference with activity; No medical intervention/therapy required
<b>Grade 2</b>	Moderate: Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
<b>Grade 3</b>	Severe: Marked limitation in activity, some assistance usually required; medical intervention/therapy required.
<b>Grade 4</b>	Potentially Life-threatening: Requires assessment in A&E or hospitalisation

## 8.6 Reporting of safety events

### Sponsor-Investigator Reporting Procedures

The Sponsor-Investigator must assess and categorise the Expedited Safety Reports received from Investigators and report these to all Site Principal Investigators, the approving HREC and Medicine and Medical Devices Regulatory Agency of Mongolia in accordance with the NHMRC's 'Safety monitoring and reporting in clinical trials involving therapeutic goods' (November 2016) and any additional requirements of the approving HREC. All safety reports must clarify the impact of the safety event on participant safety, trial conduct and trial documentation.

The Sponsor-Investigator is responsible for the following reporting to PIs, the HREC(s), the DSMB and Medicine and Medical Devices Regulatory Agency of Mongolia:

1. All SSIs that meet the definition of a USM within 72 hours of becoming aware of the issue.
2. All other SSIs within 15 calendar days of instigating or becoming aware of the issue
3. For SSIs leading to an amendment of trial documentation:
  - a. Submit details of the SSI without undue delay and no later than 15 calendar days of becoming aware of the issue.
  - b. Submit amendment to the HREC without undue delay.
4. For SSIs leading to temporary halt or early termination of a trial for safety reasons:
  - a. Communicate reasons, scope of halt, measures taken, further actions planned without undue delay and no later than 15 calendar days of decision to halt.
  - b. For a temporary halt, notify the PIs, HREC and TGA when the trial restarts, including evidence that it is safe to do so.

The Sponsor will also report SUSARs to the Medicine and Medical Devices Regulatory Agency of Mongolia as follows:

1. Fatal or life-threatening SUSARs immediately, but no later than 7 calendar days after being made aware of the issue (follow up info within a further 8 calendar days)
2. All other SUSARs no later than 15 calendar days of being made aware of the issue

The Sponsor is responsible for providing the additional safety information to the approving HREC:

1. Provide an annual safety report, including a summary of the evolving safety profile of the trial

The Sponsor is also responsible for providing any updated Product Information/Investigator's Brochure to Investigators.

## 9 DATA AND INFORMATION MANAGEMENT

The Principal Investigator is responsible for storing essential study documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

The Principal Investigator is responsible for maintaining adequate and accurate source documents that include all key observations on all participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring, and available. Changes to source data collected by the Mongolian study team must be traceable and explained in a note at relevant variables on the electronic case report form (eCRF). A site-specific Source Document Plan will be maintained to indicate the location(s) of source documents.

The Principal Investigator will maintain accurate data collection forms (known as case report forms - CRFs) and ensure that the collected and reported data is accurate, legible, complete, entered promptly, and enduring.

Any person delegated to collect data, perform data entry, or sign for data completeness will be recorded on the delegation log and trained to perform these study-related duties and functions.

Data generated for this study will be handled according to the relevant standard operating procedures (SOPs) and Data Management Plan (DMP). Full details of all processes are provided in a separate study-level DMP.

### 9.1 Data management

#### 9.1.1 Data generation (source data)

Source documents are all documents used by the investigator that relate to the participant's medical history, that verify the existence of the participant, the inclusion and exclusion criteria, and all records covering the participant's participation in the study. They include but are not limited to laboratory reports, memoranda, vaccination records, hospital records, and participant files. The site principal investigator is responsible for maintaining source documents.

An electronic CRF (eCRF) will be completed for all recruited participants.

In this study, the following types of data will be collected:

- Identifying personal information (contact details, dates of birth, home address and telephone contact and gender)
- Sensitive information, including health data (dates of COVID-19 vaccinations, medical history, primary COVID vaccine (Sinopharm (*BBIBP-CorV*®), AstraZeneca (ChAdOx1-S, or *Vaxzevria*®) or Sputnik V (Gam-COVID-Vac®)); intervention vaccine (Pfizer-BioNTech (NT162b2, or *Comirnaty*®))

- Reactogenicity information (pain, tenderness, erythema/redness, hardness, swelling, warmth, itch, fever, nausea/vomiting, diarrhoea, headache, fatigue/malaise, myalgia, arthralgia)
- Adverse events and serious adverse events
- Biological information (blood sample, immunologic assay results, including binding antibodies, functional antibodies, neutralizing antibodies, cellular immunity)

#### Source Document Plan

The source documents for this study include: COVID-19 vaccination details, date of birth, and sex); questionnaires completed by the participant and researcher (Mongolian study team's eCRF).

A Source Document Plan will be maintained to document the source (i.e., original recording) for each data discrete item/category of items collected for the study. This Source Document Plan, signed and dated by the Principal Investigator, will be prepared before recruitment of the first participant and filed in the site's Investigator Site File.

### **9.1.2 Data capture methods and data use, storage, access, and disclosure during the trial**

#### Data collection methods

Data capture and entry will be electronic. Data for this study will be collected and entered using electronic data collection forms, completed by authorised study staff and participants where applicable.

The following licensed research data collection tools will be used:

- Study data will be collected and managed using REDCap electronic data capture tools, hosted at MCRI. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. (10, 11)
- Data recorded will be linked by unique participant identifiers

Further details on the data variables are in the study DMP.

#### Use of the data

The data will be used for the analyses specified in the protocol and Statistical Analysis Plan (SAP).

Following the completion and analysis of the study, the data will be retained long-term following the mandatory archive period for use in future research projects.

#### Storage and access

---

**Study Name:** CEPI

**Protocol Number:** 81800

**Version & date:** version 7.0, dated 20 September 2023

Electronic data will be securely stored in MCRI's REDCap database system and in files stored in MCRI's network file servers, which are backed up nightly. Files containing private or confidential data will be stored only in locations accessible by appropriate designated members of the research team.

REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g., the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data creation, update, and deletion events accessible to project users who are granted permission to view it. Access to REDCap will be provided via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by and will be the responsibility of the study team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed before personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution and representatives from the HREC, Research Governance Office, and regulatory agencies may inspect all documents and records required to be maintained by the Investigator for the participants in this study. The study site will permit access to such records.

#### Disclosure

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party without the prior written approval of the sponsoring institution. Clinical information will not be released without the participant's written permission, except as necessary for monitoring by the HREC, Research Governance Office, or regulatory agencies.

#### **9.1.3 Data confidentiality**

Participant confidentiality is strictly held in trust by the Principal Investigator, participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover the testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

To preserve confidentiality and reduce the risk of identification during collection, analysis, and storage of data and information, the following will be undertaken:

- (1) The number of private/confidential variables collected for individual study participants has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.
- (2) Participant identifiers will be stored separately from the data collected, and documents with identifiers will be stored separately from participant data. Participant data and samples will be identified using a unique participant study number assigned to the study participant ("re-

identifiable”). The Principal Investigator is responsible for storing a master file of names and other identifiable data with the participant ID; access to this document will be restricted to the site study team. The master file will be stored securely and separately from study data in locked/ password-protected databases with passwords kept separately. Age and sex will be included in the data; however, it is unlikely to make specific participants or families identifiable as identifiers will be stored separately.

Separation of the roles responsible for the management of identifiers and those responsible for analysis of content. The Principal Investigator will ensure access to the data is restricted, using REDCap’s permission control functionality (“REDCap Users and Permissions”).

#### **9.1.4 Quality assurance**

Data validity and quality assurance will be ensured by the following:

- (1) Data collection and entry into the eCRF will be completed by authorised staff designated by the investigator. Appropriate training on eCRF completion will be conducted with the relevant investigator and all authorised staff before the study starts and any data is entered.
- (2) eCRFs are to be completed as soon as possible after each participant’s visit. For information collected specifically for the study, data may be entered directly to the eCRF without duplicating the information across separate source documentation and eCRF. If data are unavailable or missing, this will be indicated on the eCRF. Changes or corrections made on eCRF will be tracked via an audit trail.
- (3) Once the eCRFs have been entered, edit and consistency checks will be performed as outlined in the DMP. Data queries generated for logic and legality will be reviewed by authorised study staff for clarification. After resolving the queries, the responsible Data Manager will make the necessary updates to the database. An audit trail of all changes to the database will be maintained. Once all queries have been resolved, the database will be locked.
- (4) The Principal Investigator will be required to sign off on the eCRF data before the final database lock.
- (5) An audit is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated related activities were conducted. The data were recorded, analysed, and accurately reported according to the protocol, study SOPs, GCP, and the applicable regulatory requirement(s).

Authorised representatives of MCRI, its designee, a regulatory authority, or the IEC may visit the centre to perform audits or inspections. The investigator should contact MCRI or designee immediately if a regulatory agency contacts them about an inspection at their centre. If an audit or inspection occurs, the site PI agrees to allow the auditor/inspector direct access to all relevant documents and allocate their staff's time to the auditor/inspector to discuss findings and any relevant issues.

The statistician will be provided with anonymised data, with participants identifiable only by unique participant study number/code. The statistician will analyse the de-identified data.

### 9.1.5 Archiving - Data and document retention

#### Archiving

The Investigator will take measures to prevent accidental or premature destruction of these documents. For this study, essential documents, and data (including biological samples) will be retained for a minimum of 15 (fifteen) years post-study.

The central study site and laboratory for this study are:

- New Vaccines Research Group, Infection & Immunity, Murdoch Children's Research Institute

Records will not be destroyed without the written consent of the Principal Investigator.

#### Destruction

After the archival period of 15 (fifteen) years, The Principal Investigator will take measures to ensure secure destruction of hardcopies of study data. Any hardcopy data will be disposed of via a confidential shredding process. Noting that simply deleting files does not destroy the information, electronic CRFs will be destroyed under guidance from MCRI IT to ensure the files are permanently deleted.

The electronic, anonymised database will not be destroyed.

At the end of the archival period, eCRFs will be disposed of via secure destruction methods. Electronic databases will be retained by MCRI, stored on the secure server.

## 10 TRIAL OVERSIGHT

### 10.1 Governance structure

The Governance structure is outlined below.

#### 10.1.1 Trial Management Group (TMG)

The Site Principal Investigator is responsible for supervising any individual or party to whom they have delegated tasks at the trial site. They must provide continuous supervision and documentation of their oversight. To meet this GCP requirement, a small group will be responsible for the day-to-day management of the trial and will include at a minimum the Site PI, project manager, data manager and a representative from the Immunology team. The group will closely review all aspects of the conduct and progress of the trial, ensuring that there is a forum for identifying and addressing issues. Meetings must have minutes with attendees listed, pertinent emails retained, and phone calls documented.

#### 10.1.2 Trial Steering Committee (TSC)

A TSC will be established to provide expert advice and overall supervision and ensure that the trial is conducted to the required standards. The TSC will meet at least annually, with more frequent meetings as needed, and will work to a Terms of Reference.

### 10.1.3 Safety Monitoring

Monitoring will be performed according to Good Clinical Practice (GCP) guidelines by monitors. Following written SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. The investigator will provide direct access to all trial related source data/documents and reports for the purpose of monitoring.

#### *Independent Data Safety Monitoring Board (DSMB)*

Safety oversight will be under the direction of a DSMB. The DSMB will meet at least 6 monthly to review SAEs or AEs deemed possibly, probably or definitively related to study interventions. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons. The DSMB will meet virtually prior to the commencement of the trial then again on at least 2 occasions to review the one-month immunogenicity data for the standard and fractional-dose recipients, and to review the 6 months data. The DSMB will decide whether a fourth dose is required, based on up-to-date safety data, for participants who received a fractional dose and did not mount an adequate antibody response. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organisational meeting of the DSMB. The DSMB will be chaired by an experienced vaccine trial specialist and will contain one statistician, one adult physician and representatives from Indonesia and Mongolia. Members of the DSMB will be independent of trial conduct.

### 10.2 Site Monitoring

Trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and amendment(s), good clinical practice and applicable regulatory requirements.

Full details of trial site monitoring are documented in the Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Monitoring for this trial will be performed by the MCRI trial manager in conjunction with a Mongolian study monitor who will be trained and mentored in their role by the trial manager. The monitoring will take place on-site. The monitors will review 100% of original signed consent forms, trial eligibility data and data related to primary outcome, safety and other key data variables; review of all withdrawals from trial; targeted review of other data including investigational vaccine administration and accountability.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

### 10.3 Quality Control and Quality Assurance

Both the Sponsor-Investigator and Site Investigator have responsibilities in relation to quality management.



The Sponsor-Investigator will develop SOPs that identify, evaluate and control risk for all aspects of the trial, e.g., data management, training, eligibility, informed consent and adverse event reporting. The Sponsor-Investigator will also implement quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the study staff for clarification/resolution.

As outlined in the previous section (Site Monitoring), the trial monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Sponsor-Investigator will perform a root cause analysis and corrective and preventative action plan (CAPA).

In addition, the clinical site will perform internal quality management of trial conduct, data and biological specimen collection, documentation and completion.

## **11 STATISTICAL METHODS**

### **11.1 Sample Size Estimation**

Sample size calculations were performed using nQuery 8 software. Sample sizes per group will vary between 100 (for the AstraZeneca and Sputnik-primed groups) and 200 (for the Sinopharm-primed groups). The Sinopharm vaccinee impact is of greater importance to Mongolia as this is the main vaccine used for the primary series in Mongolia. In addition, Sinopharm is the least effective of the 3 vaccines used, so we expect to see evidence of more breakthrough cases and therefore a wider range of pre-booster immunity levels. Precision-based sample size calculations were performed based on the reactogenicity outcomes. Assuming the percentage of participants reporting local or systemic reactions is 50%, a sample size of 200 participants will produce a 95% confidence interval that extends 6.9 percentage points from the observed percentage. With a sample size of 100, the 95% confidence interval will extend 9.8 percentage points from the observed percentage. For immunogenicity, sample size calculations were based on the comparison of seroresponse rates between the standard and fractional dose groups within the non-inferiority framework. Assuming a - 10% non-inferiority margin and a seroresponse rate of 95% in both arms, the study will have >99% power for the non-inferiority comparison using 200 participants per group. Under the same assumptions, the study will have 90% power with 100 participants per group for the non-inferiority comparisons.

### **11.2 Population to be analysed**

Analysis of this trial is planned on both the intention-to-treat population (ITT), with all participants to be analysed in the group they were randomised to, as well as on the per-protocol (PP) population, consisting of participants who adhered to the study protocol. However, it is expected that withdrawn participants may not have data to contribute at all time points as blood samples may not be collected after the time of their withdrawal.

### 11.3 Methods of analysis

Reactogenicity following immunisations will be presented as the number and percentage of participants self-reporting local reactions (pain, tenderness, redness, hardness, swelling, warmth, itch at or near the injection site) and systemic reactions (fever, nausea, vomiting, diarrhoea, headache, fatigue/malaise, myalgia), and the severity of these reactions (mild, moderate, severe, life-threatening or fatal). Reactogenicity data will be presented separately by group and time point.

For immunogenicity, antibody levels will be presented as geometric mean titres (GMT) with 95% confidence intervals. Changes from baseline will be expressed as geometric mean fold ratios (GMFR), calculated as the ratio of the post-booster GMT to the baseline GMT. Seroresponse will be defined as a 4-fold rise in post-booster antibody levels compared to baseline (or >2-fold rise if the baseline (pre-booster) antibody level was  $\geq 200$  BAU/ml). To assess the non-inferiority of the fractional dose compared with the standard dose, comparisons will be based on the difference in percentage of participants with seroresponse. Using a non-inferiority margin of -10% (fractional-dose minus standard dose), non-inferiority will be declared if the lower limit of the 95% confidence interval around the difference in percentages is greater than -10%, where confidence intervals are calculated using Score-based methods (12).

Analyses will be performed using Stata software (13). Detailed methodology will be outlined in a separate Statistical Analysis Plan.

We will also do a sub-analysis to explore the difference between participants who have/haven't had previous natural infection.

#### Primary outcome (All samples at all timepoints)

The binding IgG data using the Euroimmun S1 IgG ELISA kits will be reported as relative units/ml (RU/ml) as per manufacturer's instructions. A result of <8 RU/ml: negative (IgG Antibodies for SARS-CoV-2 are not detected),  $\geq 8$  to <11 RU/ml: borderline (IgG antibodies is indeterminate/equivocal with this sample),  $\geq 11$  RU/ml: positive (IgG antibodies for SARS-CoV-2 are detected). Conversion to binding antibody units (BAU/ml) will also be done using the WHO reference serum from NIBSC, UK. Data will be presented as geometric mean titres and 95% confidence intervals.

Analysis comparing fractional and standard dose groups will be based on seroresponse rate (SRR) at 28 days post study vaccine, defined as:

- $\geq 4$ -fold rise in GMTs at 28 days post study vaccine from baseline among subjects with no pre-dose detectable titres
- $\geq 2$ -fold rise in GMTs at 28 days post study vaccine among subjects with detectable titers of  $>200$  BAU/ml pre-booster

#### Secondary outcomes

*Functional antibody (all samples at all timepoints)* – for the C-PASS assay (sVNT), data is reported as percentage (%) inhibition by neutralising antibodies using the manufacturer's instructions. A <30% inhibition is considered negative while  $\geq 30\%$  inhibition is considered positive. Data will be presented as mean and standard deviation.

*Neutralizing assay (20% subset of samples at all timepoints)* – Data will be reported as endpoint titre calculated using the Reed/Muench method (14). A titre of 10 reflects undetectable neutralizing activity.

***Cellular immunity: (on a 40% subset at six timepoints – baseline, 1 month, 6 months, 12 months, 18 months and 24 months)***

*Quantiferon COVID IFN $\gamma$  release assay* – Levels of IFN $\gamma$  will be reported in IU/ml according to manufacturer's instructions. Data will be reported as GMT and 95% confidence intervals.

*IFN $\gamma$  Elispot* – The number of IFN $\gamma$  producing cells/million PBMCs will be reported using means and 95% confidence intervals.

*Intracellular cytokine staining* – The data will be reported as frequency (%) of cytokine-expressing T cells (e.g. total T cells, CD4 T cells, CD8 T cells). Cytokines such as IFN $\gamma$  (Th1) and IL-5 (Th2) will be measured as a minimum. This will be presented as means and 95% confidence intervals.

*Multiplex cytokine assays* – A 10-plex panel of cytokines will be measured in supernatants from the Elispot studies. Cytokine concentrations will be reported in pg/ml and data presented as GMC and 95% confidence intervals.

#### **11.4 Interim Analyses**

We will conduct an interim analysis of the antibody responses from the 28 days visits to ensure that the responses in the fractional dose groups are adequate. This will be assessed on both individual and group levels by the DSMB. If fractional dose responses are considered inadequate an appropriate rescue strategy will be developed, probably involving a single dose of the vaccine in question at 3 months or as soon as the DSMB has reviewed and made a decision on the results. If the fractional dose is considered inadequate this information will be made public and shared specifically with WHO and other groups working in the field. In addition, an analysis will be undertaken once all data are collected for the 6 months analysis to review the potential need for policy changes. All such analyses will be undertaken by the trial statistician in Melbourne.

### **12 ETHICS AND DISSEMINATION**

#### **12.1 Research Ethics Approval & Local Governance Authorisation**

This protocol, the informed consent document, and any subsequent amendments will be reviewed and approved by the human research ethics committees (HREC) in Ulaanbaatar and Melbourne before the research. Letters of protocol approval by HREC will be obtained before the commencement of the trial and approval for other trial documents requiring HREC review.

#### **12.2 Amendments to the protocol**

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participant's willingness to continue participation in the trial is considered an amendment and therefore will be written and filed as an amendment to this protocol and/or informed

consent form. All such amendments will be submitted to the HREC for approval before being implemented.

### **12.3 Protocol Deviations and Serious Breaches**

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the Site Principal Investigator, who will assess for seriousness.

Those deviations deemed to affect to a significant degree the rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done promptly (Site Principal Investigator to report to the Sponsor-Investigator within 72 hours and to the Site RGO within seven days; Sponsor-Investigator to review and submit to the approving HREC within seven days).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken, and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

## **13 CONFIDENTIALITY**

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover the testing of biological samples and genetic tests in addition to the clinical information relating to participating participants.

The trial protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial, or the data will be released to any unauthorised third party without the prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and pharmacy records for the participants in this trial. The clinical trial site will permit access to such records.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the Participant Identification Number (SID) to maintain participant confidentiality.

Clinical information will not be released without the participant's written permission, except as necessary for monitoring by HREC or regulatory agencies.

## **14 PARTICIPANT REIMBURSEMENT**

Study participants will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses at each in-person visit. At the final visit (12 month or 24 month) the participant will be given a gift card for 50,000 Mongolian Tugrik (~14 USD).

## **15 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST**

No conflict of interests.

## **16 DISSEMINATION AND TRANSLATION PLAN**

Information generated by the trial will be shared at 3 levels. Participants will be given access to their personal antibody levels and to the analysed data at each of the time points once it becomes available.

The former will be on special request only, while the latter will be provided by group email as the analysed antibody data becomes available.

Interim analysis will be prepared from reactogenicity and 28-day immunogenicity data. These analyses will be presented to CEPI and WHO and shared with the authorities in Mongolia as soon as available. This will represent the first publication.

At the completion of the study a major publication will be prepared for an international journal. The data will also be presented at appropriate international conferences and meetings.

## **17 ADDITIONAL CONSIDERATIONS**

Not applicable.

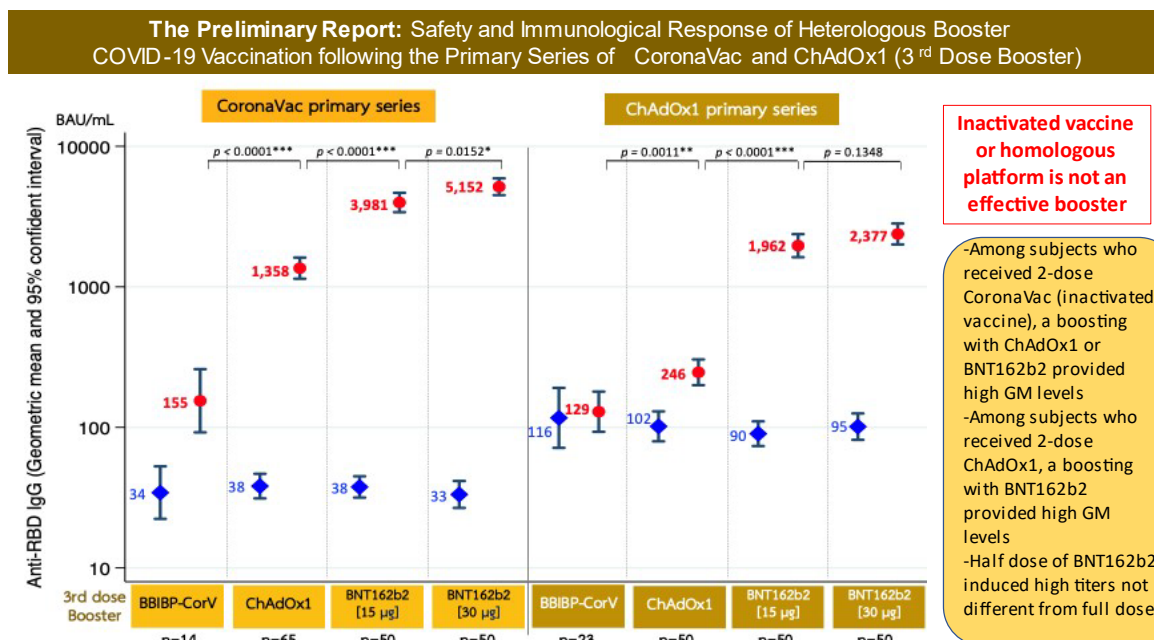
## 18 REFERENCES

1. Coalition for Epidemic Preparedness Innovations (CEPI). Priority List of Adverse Events of Special Interest: COVID-19 2020 [Available from: <https://brightoncollaboration.us/priority-list-aesi-covid/>].
2. Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. *Lancet*. 2021.
3. Indonesia reports record number of doctor deaths from COVID-19 in July [Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/indonesia-reports-record-number-doctor-deaths-covid-19-july-2021-07-18/>].
4. Sadoff J, Le Gars M, Cardenas V, Shukarev G, Vaissiere N, Heerwegh D, et al. Durability of antibody responses elicited by a single dose of Ad26.COV2.S and substantial increase following late boosting. *medRxiv*. 2021:2021.08.25.21262569.
5. Chu L, McPhee R, Huang W, Bennett H, Pajon R, Nestorova B, et al. A preliminary report of a randomized controlled phase 2 trial of the safety and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine. *Vaccine*. 2021;39(20):2791-9.
6. Dolgin E. Quarter-dose of Moderna COVID vaccine still rouses a big immune response 2021 [Available from: <https://www.nature.com/articles/d41586-021-01893-0>].
7. US Food and Drug Administration (FDA). Moderna COVID-19 Vaccine 2021 [Available from: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/moderna-covid-19-vaccine#additional>].
8. US Food and Drug Administration (FDA). Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007 [Available from: <https://www.fda.gov/media/73679/download>].
9. Australian Technical Advisory Group on Immunisation (ATAGI). ATAGI recommendations on the use of a booster dose of COVID-19 vaccine 2021 [Available from: <https://www.health.gov.au/resources/publications/atagi-recommendations-on-the-use-of-a-booster-dose-of-covid-19-vaccine>].
10. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
11. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.
12. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med*. 1998;17(8):873-90.
13. StataCorp. Stata Statistical Software: Release 17. . College Station, TX: StataCorp LLC.; 2021.
14. Juno JA, Tan HX, Lee WS, Reynaldi A, Kelly HG, Wragg K, et al. Humoral and circulating follicular helper T cell responses in recovered patients with COVID-19. *Nat Med*. 2020;26(9):1428-34.



## 19 APPENDICES

APPENDIX 1 – Pfizer half dose booster data from Thailand, courtesy of Dr Kulkanya Chokeyhaibulkit, MD, Professor of Pediatrics, Director, Siriraj Institute of Clinical Research (SICRES), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

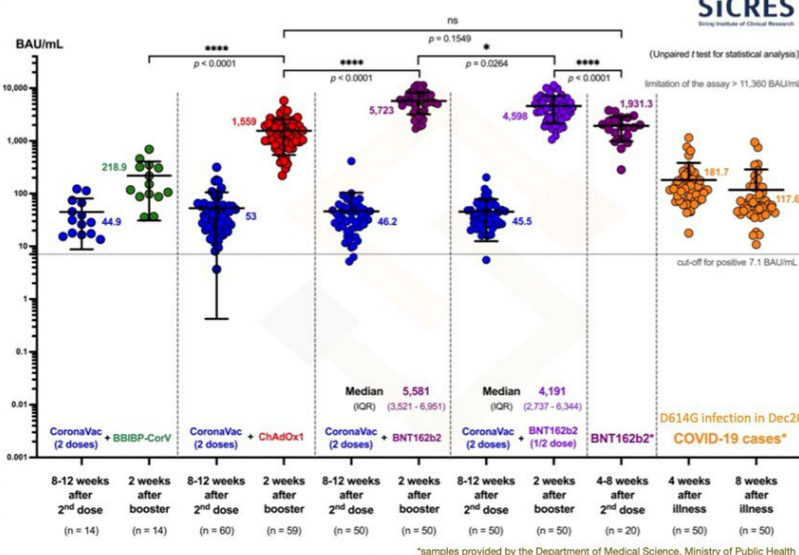


**The Preliminary Report: Safety and Immunological Response of Heterologous Booster COVID-19 Vaccination following the Primary Series of CoronaVac (3<sup>rd</sup> Dose Booster)**

Nasikarn Angkasekwinai<sup>1</sup>, Jaturong Sewatanon<sup>1</sup>, Sansanee Senawong<sup>1</sup>, Kovit Pattanapanyasat<sup>1</sup>, Suvimol Niyomnaitham<sup>1</sup>, Supakit Sirilak<sup>2</sup>, Supaporn Phumiamorn<sup>2</sup>, Sakalin Trisiriwanich<sup>2</sup>, Sompong Sapsuthipras<sup>2</sup>, Waritta Sawaengdee<sup>2</sup>, Surakameth Mahasirimongkol<sup>2</sup> and Kulkanya Chokeyhaibulkit<sup>1</sup>

<sup>1</sup>Faculty of Medicine Siriraj Hospital, Mahidol University and <sup>2</sup>Department of Medical Sciences, Ministry of Public Health

**Rationale:** The inactivated COVID-19 vaccine manufactured by Sinovac (CoronaVac) has been widely used in Thailand. The emergence of Delta variant that spread quickly, together with the report of breakthrough infections raises the concern of immunity induced by CoronaVac. Our previous report revealed low geometric mean PRNT50 titer (24.28) against Delta variant after 2-dose CoronaVac injections. From August 2021, a third dose booster has been recommended in frontline healthcare workers in Thailand who have received 2 doses of CoronaVac. We investigated the immunogenicity of a booster vaccination by heterologous platform vaccine, in particular neutralizing antibody against the Delta



**Figure 1. Quantitation of anti-SARS-CoV-2 RBD IgG determined by CMIA**

## APPENDIX 2 – Product information sheets



Product information  
sheet - Pfizer.pdf