| Protocol Number: 91108 | Statistical Analysis Plan |
|---|---|

# STATISTICAL ANALYSIS PLAN FOR:

## A randomised controlled trial to assess the immunogenicity, safety and reactogenicity of a bivalent mRNA Moderna COVID-19 vaccine or a protein-based Novavax COVID-19 vaccine given as a fourth dose in healthy adults in Australia

Trial Registration: NCT05658523

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*This document was written based on information contained in study protocol 91108 (Version 8.0, 4th December 2024).*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AIR | Australian Immunisation Register |
| BTI | Breakthrough infection |
| CMI | Cell-mediated immunity |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| GM | Geometric Mean |
| GMC | Geometric Mean Concentration |
| GMR | Geometric Mean Ratio |
| ICH | International Council for Harmonisation |
| PBMC | Peripheral blood mononuclear cells |
| PCR | Polymerase Chain Reaction |
| RAT | Rapid Antigen Test |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| MCRI | Murdoch Children's Research Institute |
| RBD | Receptor Binding Domain |
| RCH | Royal Children's Hospital |
| VoC | Variant(s) of concern |

# 1 ADMINISTRATIVE INFORMATION

Protocol: 91108; Version 8.0, 4 Dec 2024
ClinicalTrials.gov Identifier: NCT05658523

## 1.1 DOCUMENT VERSION HISTORY

| Version Date | Version | Author | Change Description | Reason/Comment |
|---|---|---|---|---|
| 19/3/2024 | 1.0 | Cattram Nguyen | Initial release. | Not applicable. |
| 20/3/2025 | 2.0 | Cattram Nguyen | Adding analysis plans for outcomes up to 30 months | Follow-up has been extended |
| | | | | |

## 1.2 SCOPE OF THIS DOCUMENT

This statistical analysis plan (SAP) outlines analyses of data up to Month 30. A previous SAP (dated 19/3/2024) focused on analyses of data up to and including Day 28 visit.

## 1.3 SUMMARY OF CHANGES COMPARED TO THE PROTOCOL

- The primary objective as worded in the protocol is to "*Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 28 days post-vaccination measured as binding antibodies (IgG ELISA – Wuhan and/or Omicron) who have been boosted at least six months earlier."* In this SAP, binding antibodies for Wuhan will be treated as the primary outcome, with other (sub)variants (e.g. Omicron BA.1 and Omicron BA.4/5) treated as secondary outcomes.
- The protocol specified that binding IgG data using the Euroimmun S1 IgG ELISA kits will be reported as relative units/ml (RU/ml) per the manufacturer's instructions, with the units converted to BAU/ml for Wuhan. Whereas they will remain RU/ml for Omicron BA.1. For the Omicron BA.4/5 binding IgG data, an in-house ELISA will be used, the units are EU/ml.
- The protocol specified two different sets of adjustment variables to be included in the linear regression model for the primary analysis of the primary immunogenicity endpoint (IgG at Day-28). In this SAP, the adjustment variables have been updated to be: age group, baseline levels, first booster vaccine and time since the first booster.

## 1.4 APPROVALS

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas. They also find it to be compliant with ICH-E9 principles and confirm that this analysis plan was developed in a completely blinded manner (i.e. without knowledge of the effect of the intervention being assessed)

| Name | Role on Study | Affiliation | Signature | Date |
|---|---|---|---|---|
| Dr Cattram Nguyen | Statistician | MCRI |  | 20/3/2025 |
| | | | | |
| | | | | |
| | | | | |

# 2 STUDY OBJECTIVES

## 2.1 PRIMARY OBJECTIVES

The primary objectives of the study (as worded in the protocol) are to:

- Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 28 days post-vaccination measured as binding antibodies (IgG ELISA – Wuhan and/or Omicron) who have been boosted at least six months earlier.
- Assess the rate and severity of reactogenicity within one-week post-second booster for the Moderna and Novavax groups (Timepoint – daily, for seven days post-vaccination).

## 2.2 SECONDARY OBJECTIVES

The secondary objectives (as worded in the protocol) are to:

- Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 28 days post-vaccination measured as functional antibodies (sVNT and nAB) and cell-mediated immunity (CMI).
- Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 6, 12, 18, 24 and 30-months post-vaccination measured as binding antibodies (IgG ELISA), functional antibodies (sVNT and nAb), and CMI.
- To describe binding and functional antibodies in the control group compared with the two vaccine groups (bivalent Moderna and Novavax) at baseline, 6, 12, 18, 24 and 30-months.
- To assess whether a fourth COVID-19 vaccine dose provides an immunological benefit over a third dose by comparing CMI at 6, 12, 18, 24 and 30-months in the control group compared with the two vaccine groups (bivalent Moderna and Novavax).
- To evaluate the safety of fourth booster dose regimens.

Exploratory objectives are:

- To describe the number and severity of breakthrough cases in the control group compared with the two vaccine groups (bivalent Moderna and Novavax) to 30 months post-vaccination.
- To correlate virological markers (viral load and viral genome characteristics) and immunological markers (humoral antibody, CMI) among mild and severe breakthrough cases.

# 3 STUDY SYNOPSIS AND BACKGROUND

*Nb. Full details of the background to the trial and its design are presented in the protocol.*

## 3.1 STUDY DESIGN

This clinical trial is a blinded, two-arm randomised study to determine the safety, reactogenicity and immunogenicity of a fourth dose of SARS-CoV-2 vaccines in Australia in adults 18 years or older who have received their third dose of COVID-19 vaccine, at least six months previously. A separate non-randomised control arm will be enrolled for comparison. The groups are described below. The trial intervention will be a single booster dose of vaccine:

| Group | Vaccine given | N |
|---|---|---|
| Group A – (Moderna) | Bivalent Moderna (mRNA-1273.214) (Ancestral SARS-CoV-2 25µg + Omicron Variant (B.1.1.529) 25µg).<br><br>Replaced by Bivalent Moderna (mRNA-1273.222) (Ancestral SARS-CoV-2 25µg + Omicron Variant (BA.4-5) 25µg) when introduced. | 225 |
| Group B – (Novavax) | Novavax (5µg of SARS-CoV-2 spike protein adjuvanted with 50µg of Matrix-M) | 225 |
| Group C – (Control group) | No vaccine given | 150 |

**Note:** Unless otherwise stated, all analyses of the Bivalent Moderna vaccine arm (Group A) will comprise data from the Moderna BA.1 and Moderna BA.4-5 groups combined.

## 3.2 STUDY GROUPS AND RANDOMISATION

The two vaccine groups (Groups A and B) will be randomised 1:1 to one of two interventions (bivalent Omicron-specific Moderna and Novavax) stratified by age (<50 and ≥50 years). An independent statistician from the Melbourne Children's Trial Centre at the Murdoch Children's Research Institute will provide a secure, password-protected web-based randomisation schedule. Blocked randomisation will be used with random blocks of permuted length.

50% of participants from each vaccine group will be included in the cell-mediated immunity (CMI) subgroup analysis. We will ensure that the age strata (<50 and ≥50 years) are equally represented in the CMI vaccine groups.

The control group will not be randomised and will be recruited from participants <60 years of age who indicate that they are not planning to receive a fourth vaccine dose at the time of recruitment. Controls will be recruited into proportional pre-defined age bands (18-29 years, 30-49 years, 50-59 years).

**Table 1. Study groups and strata**

| Group | Age group | Booster vaccine | Dose given | Number |
|---|---|---|---|---|
| **Group A** | <50 years | Bivalent Moderna BA.1 | 50μg | 75 |
| | <50 years | Bivalent Moderna BA.4-5 | 50μg | 75 |
| | ≥50 years | Bivalent Moderna BA.4-5 | 50μg | 75 |
| **Group B** | <50 years | Novavax | 50μg | 150 |
| | ≥50 years | Novavax | 50μg | 75 |
| **Group C** | <60 years | No vaccine | - | 150 |

### 3.3 BLINDING

Study staff involved in administering the vaccine will use REDCap to receive the information on the participant's randomisation (study ID) number and vaccine. Study staff will upload vaccination information to the Australian Immunisation Register (AIR) after one week. Participants will remain blinded to their vaccine type until day seven post-vaccination when their vaccination history is uploaded to the AIR. Study staff assessing reactogenicity and immunogenicity will be blinded to each participant's vaccine allocation, which will be hidden in REDCap for blinded study staff. Statisticians and analysts will remain blinded during the development of the SAP and will develop and finalise all codes using a dummy variable for treatment allocation.

### 3.4 STUDY POPULATION: ELIGIBILITY AND SCREENING

The trial population will be adults 18 years and older who have been boosted at least six months earlier with a third COVID-19 vaccine dose. There will be no upper age limit for groups A (Moderna) and B (Novavax). Only those aged >18 - <60 years will be recruited to group C (controls), as this is the target age group for which the need for additional boosters is not well established. Additional booster doses are strongly recommended for individuals 60 years and over. Procedures will be implemented to ensure an even age distribution for Moderna product transition in each vaccine group.

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

1. Have received a third COVID-19 vaccine dose at least six months before the start of the study.
2. No confirmed SARS-CoV-2 infection by PCR or RAT within the last three months.
3. Willing and able to give written informed consent.
4. Aged 18 years or above.
5. Willing to complete the follow-up requirements of the study.

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

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

1. Currently receiving immunosuppressive medication or anti-cancer chemotherapy.
2. Known HIV infection.
3. Congenital immune deficiency syndrome.
4. Received immunoglobulin or other blood products in the three months prior to potential study booster vaccination.
5. Study staff and their relatives.

6. Have a history of a severe allergic reaction to any COVID-19 vaccines or have a medical exemption to receiving further COVID-19 vaccines.
7. Cannot read or understand English.

### 3.5 SAMPLE SIZE

Sample size calculations were performed using nQuery 8 software and methods described by Van Belle, et al. 1993 (20). Precision-based sample size calculations were performed based on the reactogenicity outcomes. Assuming the percentage of participants reporting local or systemic reactions is 50%, 100 participants will produce a confidence interval that is 9.8 percentage points from the observed percentage. For immunogenicity, sample size calculations were based on comparing day 28 post-booster geometric mean concentrations of IgG antibodies between vaccine arms. We assumed the coefficient of variation (standard deviation/mean) of the post-booster antibody concentrations would be 1.15 (based on data from Munro, et al. 2021 (8), but increased to be conservative). Even though previous studies demonstrated a geometric mean ratio (GMR) of up to 4 between the study vaccine groups, we considered a clinically important difference between groups to be a GMR of >1.4. Based on these assumptions, the study will need to recruit 160 participants in each vaccine group overall to achieve 90% power at a two-sided 0.05 significance level. Allowing for ~20% loss to follow-up, the sample size in each arm was expanded to 200. To ensure age representation (<50 and ≥50) in the second Moderna bivalent group (BA.4-5) numbers were increased in the younger age group. We are confident that the sample size is sufficient as it is likely that the magnitude of the GMR will be higher than expected and the loss to follow-up lower than anticipated. Note that the original sample size was 200 per group, which changed to 225 in each vaccine group and 150 in the control group.

### 3.6 STUDY PROCEDURES

Table 2 provides a summary of the study procedures. A participant will be considered lost to follow-up if they fail to return for two consecutive visits and cannot be contacted by the trial staff.

**Table 2. Schedule of assessments**

| **Assessments/ activities*** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 7** |
|---|---|---|---|---|---|---|---|
| Timing | Day 0 | Day 1 | Day 7 | Day 28 | 3 months | 6 months | 12 months |
| Visit window | | | + 3 days | - 3 days<br>+ 7 days | +/-<br>14 days | +/-<br>14 days | +/-<br>14 days |
| Group | A,B,C | A,B | A,B | A,B,C | A,B,C | A,B,C | A,B,C |
| Location of visits | At RCH | Phone call | Phone call | At RCH (A,B)<br>Phone call (C) | Phone call | At RCH | At RCH |
| Informed consent | X | | | | | | |
| Eligibility confirmation | X | | | | | | |
| Randomisation | X (A,B) | | | | | | |
| Blood sampling | X | | | X (A,B) | | X | X |
| Vaccination | X (A,B) | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Vital signs | X (A,B) | | | | | | |
| Issue diary card, ruler, and thermometer | X (A,B) | | | | | | |
| Collect diary card | X (daily) for vaccine groups (A&B) | | | | | | |
| 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 SARS-COV-2 infection/ COVID-19 | Throughout study period | | | | | | |

*****Unless otherwise indicated, assessments/activities are valid for Groups A, B and C.

# 4 GENERAL STATISTICAL METHODOLOGY

## 4.1 OBJECTIVES OF THE ANALYSIS PLAN

This analysis plan covers analyses for the primary and secondary objectives, and analyses of breakthrough infections. Analyses of other exploratory objectives will be detailed in a separate plan.

## 4.2 STATISTICAL SOFTWARE

All analyses will be conducted using Stata Version 18.0.

## 4.3 VALIDATION OF RESULTS

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

## 4.4 ANALYSIS POPULATIONS

See Estimand-to-Analysis tables for further information on analysis populations.

## 4.5 MULTIPLICITY ADJUSTMENT

This trial will evaluate multiple outcomes, including multiple (sub)variants for the immunogenicity outcomes (Wuhan, Omicron BA.1, Omicron BA.4/5, Omicron JN.1). To avoid multiple primary outcomes, this SAP has specified binding antibody levels (IgG) for the Wuhan strain at Day-28 as the primary immunological endpoint. For group comparisons, treatment effects with 95% confidence intervals will be presented. Results will be interpreted based on the magnitude of the treatment effects. No multiplicity adjustments have been planned.

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

## 4.6 INTERIM ANALYSES

There will be no interim analyses, however see Section 4.8 for planned Timing of analyses.

## 4.7 REPORTING

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

## 4.8 TIMING OF ANALYSES

Due to the rapidly evolving nature of the pandemic, analyses will be conducted for each immunological endpoint once the necessary data have been cleaned and locked, which will be as soon as is practicable after all participants have completed their Day-28 visit (for Day-28 endpoints), Month-6 visit (for Month-6 endpoints), Month-12 visit (for Month-12 endpoints), Month-18 (for Month-18 endpoints) and Month-24 (for Month-24 endpoint), although some of the longer-term endpoints (e.g. Month-6 and Month-12 results) may be published together. Necessary data for analysis includes those required for the reactogenicity, safety, breakthrough infection endpoints, and data on intercurrent events to the same timepoint as for the

immunological endpoint to be analysed, as these are essential for interpretation. A list of necessary variables is provided in Section 4.9.

### 4.9 LIST OF NECESSARY VARIABLES

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

- Trial arm
- Primary series vaccine
- First booster vaccine
- Age group strata
- Dates of first, second and third doses
- Date of trial vaccine for vaccine groups (Day 0)
- Date of blood-draw/study visit
- Reactogenicity for all solicited reactions on 7 days, including grading (Day-28 timepoint only)
- SARS-CoV-2 infection, including clinical spectrum and date of positive test (to relevant timepoint)
- Receipt of additional COVID-19 vaccine doses (yes/no, and date) (to relevant timepoint)
- Adverse events (severity, causality, SOC, seriousness, expectedness, and outcome) (to relevant timepoint)
- Baseline value of the immunological parameter to be analysed

### 4.10 HANDLING OF MISSING DATA

*Exploration of missing data*
The number and percentage of participants with missing data will be reported by study arm at each time point. Baseline characteristics of participants with and without missing data will be tabulated. To explore differential drop-out/withdrawal and trajectories of immunological endpoints by withdrawal status, we will plot antibody titres (Wuhan) over time by strata defined by time of withdrawal (separately by trial group).

Multiple imputation will be performed for the primary analysis of immunological endpoints if more than 5% of participants have missing data. Multiple imputation will be performed using multivariate imputation by chained equations (MICE), with logistic regression for binary variables and linear regression for continuous variables (or predictive mean matching if non-normal). Missing values will be imputed separately by trial arm to ensure treatment effects are maintained, and 50 imputations will be produced. The imputation model will include all variables that are included in the primary analysis model, including stratification variables (age group) and baseline levels of the outcome variable. Covariates considered for inclusion in the imputation model as auxiliary variables include primary series vaccine, duration between different doses and study day of blood draw. Where possible, multiple imputation will be performed simultaneously for all immunological outcomes, but it may be necessary to use separate models at different timepoints due to the timing of analyses. The same imputation models will be used for data set to missing for analyses under the hypothetical strategy. See Estimand-to-Analysis tables under specific outcomes for further detail regarding handling of missing data.

### 4.11 DEFINITIONS RELATED TO ESTIMANDS

Sections 7 and 8 specify analytical approaches for the primary and secondary endpoints using the estimand framework. An estimand is a precise description of the quantity that is estimated to assess the treatment effect reflecting the clinical question posed by a given clinical trial objective. It has five attributes: population,

treatment, variable of interest, e.g., outcome and timepoint, summary measure, and possible intercurrent events (defined as an event that can occur post-randomisation and preclude or affect the interpretation of the variable of interest, e.g. discontinuation of treatment). Intercurrent events specific to this trial are described in Section 6.5, 'Intercurrent events'.

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

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

### 4.12 ESTIMAND-TO-ANALYSIS TABLES

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

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

# 5 DESCRIPTIVE STATISTICS

## 5.1 PARTICIPANT DISPOSITION

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

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

*[Subsequent numbers will be given by study group]*

- Allocated to each study group
  - and received the allocated vaccine
  - and did not receive the allocated vaccine*
- Included in the Reactogenicity and Safety Population (according to vaccine received not allocated)^
- Included in the Primary Day-28 Immunology Population^
- Included in the Month-6 Immunology Population^
- Included in the Month-12 Immunology Population^

* *Reasons will be provided.*

^*The number of participants with missing data will be noted. Missing data arising from lost-to-follow-up or withdrawal will be enumerated, including the level of withdrawal (from intervention, follow-up, or both, and consent to use data up to the time of withdrawal) and reasons (harms-related reasons for withdrawal will be emphasised).*

## 5.2 PATIENT CHARACTERISTICS AND BASELINE COMPARISONS

Baseline and demographic characteristics, including stratifying variable (age group) will be described by study group; see Dummy Table 1. Categorical variables will be described with the number in each category and corresponding percentage of the whole study group. Normally distributed continuous variables will be described by the mean, standard deviation, and minimum and maximum values. Non-normally distributed continuous variables will be described by the median, $25^{th}$ and $75^{th}$ percentiles, and minimum and maximum values. Statistical tests for differences between study groups at baseline will not be performed.

## 5.3 ADHERENCE AND PROTOCOL DEVIATIONS

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

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

- Inclusion and randomisation of an ineligible person
- Receiving the wrong trial vaccination
- Day-28 visit occurring outside of the specified time window (between Day 25 and 35 [inclusive], with Day 0 being the day of trial vaccination)

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

### 5.4 CONCOMITANT MEDICATIONS

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

# 6 OUTCOME VARIABLES AND OTHER PARAMETERS

## 6.1 OUTCOME VARIABLES AS DEFINED IN THE PROTOCOL

### 6.1.1 Primary outcomes

The primary outcomes (as defined in the protocol) are:

Immune response

*Binding antibodies* – These will be evaluated using the commercial Euroimmun S1 IgG ELISA (Wuhan and Omicron [once available]) on serum collected at four timepoints (baseline, 28 days, 6 months, and 12 months) for the two vaccine groups and three timepoints (baseline, 6 months, and 12 months) for the control group.

Reactogenicity

Reactogenicity for vaccine groups (A&B) will be measured using the accepted standardised method to evaluate systemic and local side effects following vaccination using a structured questionnaire for seven days post-vaccination, as outlined in Table 1 in the protocol.

### 6.1.2 Secondary outcomes

The secondary outcomes (as defined in the protocol) are:

**Immunogenicity**

- Functional antibody – All samples will be assayed using the GenScript cPass SARS-CoV-2 Neutralization Antibody detection kit for WT and Omicron variant RBD antigen or other key newly emerging variants. Samples will be tested on serum collected at four timepoints (baseline, 28 days, 6 months, and 12 months) for the two vaccine groups and three timepoints for the control group.
- Neutralising antibody - A fraction of samples (20%) will be assessed using a SARS-CoV-2 assay at the PDI, Melbourne. Testing will be at the same time points as for binding antibodies for Wuhan strain and two Variants of Concern (VoC), including Omicron or other key newly emerging variants.
- Cellular immunity - Cellular immunity will be assessed on 50% of participants per group of samples collected at four timepoints for the two vaccine groups and three timepoints for the control group as follows:
    - QuantiFERON Human IFN-γ SARS-CoV-2 (Qiagen) will be performed using heparinised whole blood (Wuhan).
    - Peripheral blood mononuclear cells (PBMCs) will be isolated by density gradient centrifugation within 12 hours of collection and stored in liquid nitrogen at MCRI. Assays will include IFN-γ Elispot, intracellular cytokine assays (flow cytometry) and multiplex cytokine assays (Wuhan and Omicron).

**Safety**

All solicited AEs will be collected for 7 days, all unsolicited AEs will be collected for 28 days, and all medically attended AEs will be collected for 3 months. SAEs will be collected throughout the 12-month follow-up period.

### 6.1.3 Exploratory outcomes

The exploratory outcomes (as described in the protocol) are:

- Previous infections (RAT or PCR positive or symptomatic with close contact) and vaccinations will be recorded at baseline.

- Breakthrough infections will be recorded and tested for during the study.
- Nasal swabs will be collected from all severe breakthrough cases and a subset of mild cases within three days of illness. A representative sample of positive samples will be processed for viral load and whole genome sequencing of SARS-CoV-2.
- We will explore differences in viral load, genome characteristics, and immunological markers among mild and severe breakthrough cases.

### 6.2 IMMUNOGENICITY OUTCOME VARIABLES

Table 3 lists the immunogenicity outcome variables including the units, and participant subsets in which the outcomes are measured. There may be additional immunogenicity outcome variables (e.g. for additional variants) that may become available after this SAP is written.

**Table 3. Description of immunogenicity outcome variables, including units and subsets in which they are measured**

| | Outcome | Subset | Units |
|---|---|---|---|
| Main study | Binding antibody (IgG) (Euroimmun Wuhan) | All | BAU/ml |
| | Binding antibody (IgG) (Euroimmun Omicron BA.1) | All | RU/ml |
| | Binding antibody (IgG) (In-house assay Omicron BA.4/5) | All | EU/ml |
| | Binding antibody (IgG) (In-house assay Omicron JN.1) | All | EU/ml |
| | Binding antibody (IgG) (N-Protein) | All | EU/ml |
| | Functional antibody (C-PASS assay - sVNT Wuhan) | All | U/mL |
| | Functional antibody (C-PASS assay - sVNT Omicron BA.1) | All | U/mL |
| | Functional antibody (C-PASS assay - sVNT Omicron BA.4/5) | All | U/mL |
| | Neutralising antibody (Wuhan) | 20% of samples | NT50 |
| | Neutralising antibody (variant of concern)* | 20% of samples | NT50 |
| CMI sub-study | IFNγ | 50% of participants | IU/ml |

^Baseline measurements are also taken at Day 0

* Variants of concern to be confirmed

### 6.3 REACTOGENICITY AND SAFETY OUTCOMES

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

**Table 4. Reactogenicity and safety outcomes**

| Outcome | Parameter | Categories | Timepoints |
|---|---|---|---|
| Reactogenicity (local) | Pain | | |

| | | | |
|---|---|---|---|
| | Tenderness | Grade 0, 1, 2, 3, or 4* | Day 1, 2, 3, 4, 5, 6, & 7 |
| | Redness | | |
| | Swelling | | |
| | Hardness | | |
| | Axillary lymphadenopathy | | |
| | Warmth | Binary (presence/absence) | |
| | Itch | | |
| Reactogenicity (general/systemic) | Fever | Grade 0, 1, 2, 3, or 4* | |
| | Nausea | | |
| | Vomiting | | |
| | Diarrhoea | | |
| | Headache | | |
| | Fatigue/Malaise | | |
| | Myalgia | | |
| | Arthralgia | | |
| Adverse Events to 28 Days<br><br>Adverse Reaction to 28 Days[δ]<br><br>Serious Adverse Events to 12 months | Experienced an adverse event | Binary (yes/no) | Adverse Events to 28 Days: Day-0, -1, -7, and -28 visits, and Month-3 visit (for new information, e.g., resolution)<br><br>Serious Adverse Events to 12 months: Unscheduled (participants instructed to contact study staff) |
| | System Organ Class^ | As per MedDRA | |
| | Severity | Severity Grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (fatal)[#] | |
| | Outcome | 1-Resolved<br>2-Resolved with sequelae<br>3-Ongoing<br>4-Fatal<br>5-Unknown | |
| | Serious | Binary (yes/no) | |
| | Onset (days from trial vaccination) | *Continuous* | |
| | Event duration (days) | *Continuous* | |
| | Relatedness | 1-Unrelated<br>2-Possible<br>3-Probable<br>4-Definite | |

*5-point severity scale: 0-None; 1-Mild; 2-Moderate; 3-Severe; 4-Life-threatening. *Refer to Protocol for more detailed definitions* [#]Grade 3-4 events may be SAEs; all Grade 5 events are automatically considered SAEs. ^Will require derivation from 'event_term' and 'saefin' fields by study team. [δ]An adverse reaction is an adverse event with causality assessment of either Possible, Probable, or Definite.

### 6.4 DEMOGRAPHY AND BASELINE VARIABLES

At the Day 0 visit, information is collected on the participant's previous COVID-19 vaccines (including vaccine, dates, and any reactions experienced), history of previous SARS-CoV-2 infections, demographics (e.g. age, sex, ethnicity), comorbidities, and clinical observations before trial vaccination. Details of demography and baseline parameters are stored in RedCAP Codebooks.

### 6.5 INTERCURRENT EVENTS

Data will be collected throughout the 12-month follow-up period on receipt of COVID-19 vaccines (including date and vaccine) and breakthrough SARS-CoV-2 infections (including date and severity). These will be considered intercurrent events in the analysis; the strategies used for handling these events are detailed in Estimand-to-Analysis tables in Sections 7 and 8. Intercurrent event parameters are detailed below:

| **Intercurrent event** | **Potential impact if ignored** |
|---|---|
| Breakthrough SARS-CoV-2 infection | Breakthrough infections will have a boosting effect on immunological markers, making the trial vaccine appear more immunogenetic than it truly is. High incidence of breakthrough infections due to reduced immunogenicity in one group could give the appearance of greater immunogenicity of the trial vaccination in this group relative to other groups in which breakthrough infections have been more successfully prevented. |
| Receipt of 5$^{th}$ dose (self-initiated) | Receipt of a 5$^{th}$ dose will have a boosting effect on immunological markers, making the trial vaccine appear more immunogenetic than it truly is. Higher uptake of the 5$^{th}$ dose in one group could give the appearance of greater immunogenicity of the trial vaccination in this group relative to other groups with lower 5$^{th}$ dose uptake. |

Lost-to-follow-up and other events resulting in missing data will be treated as a missing data problem (see Section 4.10 "Handling of missing data".

# 7 ANALYSIS OF THE PRIMARY OUTCOMES

## 7.1 PRIMARY ENDPOINTS

### 7.1.1 Immune response at Day-28

The primary endpoint is binding antibody at the Day 28 visit for Wuhan (BAU/ml) as evaluated using the Euroimmun S1 IgG ELISA, comparing the two vaccine groups (Groups A and B).

### 7.1.2 Reactogenicity within 7 days of boosting

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

Table 5 outlines the primary endpoints, including the timepoint, population summary measure, comparison groups and measure of association.

**Table 5. Primary endpoints**

| Primary Endpoint | Outcome | Timepoint | Population measure | Comparison | Measure of association |
|---|---|---|---|---|---|
| i. | Binding antibody for Wuhan | Day-28 visit | Geometric mean concentration (GMC) (95% CI) | Group A vs Group B (Nb. Group A consists of Moderna BA.1 and BA.4-5 combined) | Geometric mean ratio (GMR) |
| ii. | Reactogenicity: solicited grade 3 or 4 local or systemic reactions within 7 days of vaccination, inclusive | 7 days post-booster | % (95% CI) | NA (descriptive) | NA (descriptive) |

## 7.2 MAIN ANALYSIS OF THE PRIMARY ENDPOINTS

Table 6 and Table 7 are the Estimand-to-analysis tables for the primary immunological and reactogenicity endpoints, respectively.

**Table 6.** Estimand-to-Analysis table[5] for immune response (binding antibodies- IgG) at Day-28 (primary immunogenicity endpoint)

<table>
<tr><td colspan="3">Primary Objective (as per Protocol):<br>Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 28 days post-vaccination measured as binding antibodies (IgG ELISA – Wuhan) who have been boosted at least six months earlier.</td></tr>
<tr><td colspan="2">Estimand:</td><td>Geometric mean ratio (GMR) of binding antibodies (IgG ELISA – Wuhan) 28 days post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax) in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of SARS-CoV-2 infection.</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment<br>Bivalent mRNA Moderna COVID-19 vaccine and protein-based Novavax COVID-19 vaccine</td><td>Study arms<br>Bivalent Moderna vaccine arm (Moderna BA.1 and Moderna BA.4-5 groups combined)<br>Novavax vaccine arm</td></tr>
<tr><td colspan="2">Target population<br>Adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously</td><td>Analysis set (“Primary Day-28 Immunology Population”)<br>All randomised participants as per randomisation with complete outcome and covariate data</td></tr>
<tr><td colspan="2">Variable<br>Binding antibodies (IgG ELISA for Wuhan, Omicron BA.1 and Omicron BA.4/5) 28 days after trial vaccination</td><td>Outcome measure<br>Geometric mean concentrations of binding antibodies at the Day-28 visit (25 – 35 days post-booster)</td></tr>
<tr><td colspan="2">Handling of intercurrent events</td><td rowspan="3">Handling of missing data<br>The proportion of participants excluded due to missing outcome or covariate data will be described by study group.<br><br>If >5% of participants are excluded due to missing data, a supplementary analysis will be performed with multiple imputation.</td></tr>
<tr><td>Event (up to and including Day-28 visit)</td><td>Strategy[4]</td></tr>
<tr><td>SARS-CoV-2 infection</td><td>Treatment Policy[#] (interpret results in conjunction with breakthrough infection rates)</td></tr>
<tr><td colspan="2">Population-level summary measure<br>Geometric mean ratio</td><td>Analysis approach<br>Linear regression will be used to estimate the GMR comparing the two vaccine groups, adjusted for the stratifying variable (age group), baseline levels, first booster vaccine and time since first booster. The outcome variable (and the baseline value) will be $\log_e$ transformed before regression, and the GMR (95% CI) will be calculated as the antilogarithms of the mean difference ($\beta_1$) and it’s 95% CI.</td></tr>
</table>

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

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

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Assess the rate and severity of reactogenicity within one-week post-second booster for the Moderna and Novavax groups (Timepoint – daily, for seven days post-vaccination).</td></tr>
<tr><td colspan="2">Estimand:</td><td>Incidence risk of a grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting, by vaccine group in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment<br>Bivalent mRNA Moderna COVID-19 vaccine and protein-based Novavax COVID-19 vaccine</td><td>Study arms<br>Bivalent Moderna vaccine arm (Moderna BA.1 and Moderna BA.4-5 groups combined)<br>Novavax vaccine arm</td></tr>
<tr><td colspan="2">Target population<br>Adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously</td><td>Analysis set (“Reactogenicity Population”)<br>All participants, as per trial vaccine received (regardless of allocation).</td></tr>
<tr><td colspan="2">Variable<br>Grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td><td>Outcome measure<br>Presence of at least one solicited grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td></tr>
<tr><td colspan="2">Handling of intercurrent events<br><table><tr><td>Event (up to and including Day-7)</td><td>Strategy[4]</td></tr><tr><td>SARS-CoV-2 infection</td><td>While Negative (values up to the day of the first positive test are used)</td></tr><tr><td>Death</td><td>While Alive (values up to the time of death are used)</td></tr></table></td><td>Handling of missing data<br>It will be assumed that participants with missing reactogenicity datapoints (collected daily for each reaction type) did not experience the specific reaction on the day/s where the value is missing. Missing data by day and reaction will be described by study group.</td></tr>
<tr><td colspan="2">Population-level summary measure<br>Incidence risk (proportion) of at least one solicited grade 3 or 4 local or systemic reaction within 7 days (inclusive) of boosting.</td><td>Analysis approach<br>Proportions will be estimated with 95% Clopper-Pearson binomial confidence intervals using the ci Stata command.<br><br>Supplementary analysis:<br>The following reaction-specific descriptive analyses will also be conducted:<br>• Number and percentage of individuals with each reaction type, presented in a radial graph (Dummy Figure 2).<br>• Number and percentage of participants with each reaction type, by severity grade (Dummy Figure S 1).<br>• Distribution of the day of onset for each reaction type<br>• Distribution of the duration of each reaction type</td></tr>
</table>

# 8 ANALYSIS OF THE SECONDARY OUTCOMES

## 8.1 ANALYSIS OF SECONDARY IMMUNOLOGICAL ENDPOINTS

Table 8 lists the secondary immunological endpoints, including the timepoint measured, population measure, groups being compared and the measure of association between groups. Note there may be additional secondary immunological outcome variables (e.g. relating to new variants of concern) that become available after this SAP is written. These additional variables will be analysed in the same way as other secondary immunological variables listed in Table 8, with analysis dependent on the distribution (e.g. whether symmetrical).

**Table 8. Secondary immunological endpoints**

| Outcome | Population measure | Measure of association | Timepoint | Comparisons |
|---|---|---|---|---|
| **Binding antibody** | | | | |
| Binding antibody (IgG) (Wuhan) BAU/ml | GM (95% CI) | GMR (95% CI) | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| Binding antibody (IgG) (Omicron BA.1), RU/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| Binding antibody (IgG) (Omicron BA.4/5), EU/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| Binding antibody (IgG) (Omicron JN.1), EU/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| **Functional antibody** | | | | |
| Functional antibody sVNT (Wuhan), U/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| Functional antibody sVNT (Omicron BA.1), U/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| Functional antibody sVNT (Omicron BA.4/5),U/ml | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-18 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-24 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-30 | Group A vs B, Group A vs control, Group B vs control |
| **Neutralising antibody** | | | | |
| Neutralising antibody (Wuhan), NT50 | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |

| | | | | |
|---|---|---|---|---|
| Neutralising antibody (variant of concern)#, NT50 | GM (95% CI) | GMR (95% CI) | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| **Cellular mediated immunity** | | | | |
| Ag1 IFNγ (IU/ml) | GM (95% CI) or median (95% CI)^ | GMR (95% CI) or difference in medians (95% CI)^ | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |
| Ag2 IFNγ (IU/ml) | GM (95% CI) or median (95% CI)^ | GMR (95% CI) (95% CI)^ | Day-28 | Group A vs B |
| | | | Month-6 | Group A vs B, Group A vs control, Group B vs control |
| | | | Month-12 | Group A vs B, Group A vs control, Group B vs control |

GM: Geometric mean. GMR: Geometric mean ratio

#variants of concern for neutralising antibody to be confirmed

^Data will summarised using medians, and compared across groups using difference in medians in the case of negative and zero values and log-transformation not possible

### 8.1.1 Estimand-to-Analysis tables for secondary immunological endpoints

**Table 9.** Generic Estimand-to-Analysis table for all secondary Day-28 immunological endpoints (specified in Table 8).

| **Objectives (as per Protocol):** Assess and compare the immune response in two randomised vaccine groups (bivalent Moderna and Novavax) at 28 days post-vaccination, measured as functional antibodies (sVNT and nAb) and cell-mediated immunity (CMI). | |
|---|---|
| Estimand: | [Measure of Association]* of [OUTCOME]* 28 days post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax) in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of SARS-CoV-2 infection. |
| **ESTIMAND Attributes:** | **Incorporation of Estimand Attribute in ANALYSIS:** |
| **Treatment**<br>Bivalent mRNA Moderna COVID-19 vaccine and protein-based Novavax COVID-19 vaccine | **Study arms**<br>Bivalent Moderna vaccine arm (Moderna BA.1 and Moderna BA.4-5 groups combined)<br>Novavax vaccine arm |
| **Target population**<br>Adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously | **Analysis set ("Secondary Day-28 Immunology Population")**<br>All randomised participants as per randomisation with complete outcome and covariate data |
| **Variable**<br>[OUTCOME]*, 28 days after boosting. | **Outcome measure**<br>[OUTCOME]* at the Day-28 visit (25 – 35 days post-booster). |
| **Handling of intercurrent events**<br>*Event (up to and including Day-28 visit)* — *Strategy*[4]<br>SARS-CoV-2 infection — Treatment Policy# (interpret results in conjunction with breakthrough infection rates) | **Handling of missing data**<br>The proportion of participants excluded due to missing outcome or covariate data will be described by study group.<br>If >5% of participants are excluded due to missing data, a supplementary analysis will be performed with multiple imputation. |
| **Population-level summary measure**<br>Geometric mean ratio (GMR) OR Difference in Means* | **Analysis approach**<br>Linear regression will be used to estimate the difference in mean [OUTCOME]* between the vaccine arms, adjusted for the stratifying variable (age group), |

| | |
|---|---|
| | first booster vaccine, time since first booster vaccine and baseline [OUTCOME]* levels.<br><br>Where the population-level summary measure is the GMR, the outcome variable (and the baseline value) will be $\log_e$ transformed prior to regression, and the GMR (95% CI) will be calculated as the antilogarithms of the mean difference ($\beta_1$) and it's 95% CI.<br><br>When zero and negative values are expected, the population-level summary measure will be the difference in medians. This will estimated using quantile regression with the same adjustment variables as above.<br><br>**Planned figures**<br>The distribution of the immunological data will be displayed using a scatterplot overlaid with median and interquartile range (see Dummy Figure 3) |

**This table is generic for all secondary Day-28 immunological endpoints (see **Table 8**, which will be analysed in the same way depending on their distributions; the population measure for outcomes with skewed distributions is the geometric mean and the population-level summary measure of association is the GMR – baseline and Day-28 values will be $\log_e$ transformed prior to analysis*

**Table 10.** Generic Estimand-to-Analysis table for all secondary Month-6, Month-12, Month-18 and Month-24 immunological endpoints (specified in Table 8).

<table>
<tr><td colspan="3">Primary Objective (as per Protocol): Compare the immunogenicity in two randomised vaccine groups (bivalent Moderna and Novavax) at 6, 12, 18, 24, 30 months post-vaccination.</td></tr>
<tr><td colspan="2">Estimand:</td><td>[MoA]* of [OUTCOME]* 6/12/18/24/30 months post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax) in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of SARS-CoV-2 infection or receipt of a 5th dose (self-initiated).</td></tr>
<tr><td colspan="2">ESTIMAND Attributes:</td><td>Incorporation of Estimand Attribute in ANALYSIS:</td></tr>
<tr><td colspan="2">Treatment<br>Bivalent mRNA Moderna COVID-19 vaccine and protein-based Novavax COVID-19 vaccine</td><td>Study arms<br>Bivalent Moderna vaccine arm<br>Novavax vaccine arm</td></tr>
<tr><td colspan="2">Target population<br>Adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously</td><td>Analysis set (“Month-6/12 Immunology Population”)<br>All randomised participants as per randomisation with complete outcome and covariate data</td></tr>
<tr><td colspan="2">Variable<br>[OUTCOME]*, 6/12 months after boosting.</td><td>Outcome measure<br>[OUTCOME]* at the Month-6/12 visit (6/12 months +/- 14 days post-booster).</td></tr>
<tr><td colspan="2">Handling of intercurrent events<br><table><tr><td>Event (up to and including Month-6/12 visit)</td><td>Strategy[4]</td></tr><tr><td>SARS-CoV-2 infection at any time</td><td>Treatment Policy (interpret results in conjunction with breakthrough infection rates)</td></tr><tr><td>Receipt of 5th dose (self-initiated)</td><td>Treatment Policy (interpret results in conjunction with 5th dose coverage)</td></tr></table></td><td rowspan="2">Handling of missing data<br>The proportion of participants excluded due to missing outcome or covariate data will be described by study group.<br><br>If >5% of participants are excluded due to missing data, a supplementary analysis will be performed with multiple imputation.</td></tr>
<tr><td colspan="2">Population-level summary measure<br>Geometric mean ratio (GMR) OR Difference in Means*</td></tr>
<tr><td colspan="2"></td><td>Analysis approach<br>Linear regression will be used to estimate the difference in mean [OUTCOME]* between the vaccine arms, adjusted for the stratifying variable (age group), primary series and first booster vaccine, and baseline [OUTCOME]* levels.<br><br><u>Where the population-level summary measure is the GMR,</u> the outcome variable (and the baseline value) will be $\log_e$ transformed before regression, and the GMR (95% CI) will be calculated as the antilogarithms of the mean difference ($\beta_1$) and it’s 95% CI.<br><br><u>When zero and negative values are expected, the population-level summary measure will be the difference in medians.</u> This will estimated using quantile regression with the same adjustment variables as above.<br><br>The distribution of the immunological data at each timepoint will be displayed using a scatterplot</td></tr>
</table>

| | |
|---|---|
| | overlaid with median and interquartile range (see Dummy Figure 3) |

*This table is generic for all secondary Month-6 and Month-12 immunological endpoints (see Table 8), which will be analysed in the same way depending on their distributions; the population measure for outcomes with skewed distributions is the geometric mean and the population-level summary measure of association (MoA) is the GMR – baseline and Month-[6/12] values will be $\log_e$ transformed before analysis; the population measure for normally distributed outcomes is the mean and the population-level summary measure of association (MoA) is the Difference in Means. For outcomes with skewed distributions and negative values, the population summary measure of association is the difference in medians, which will be estimated using quantile regression.

## 8.2 ANALYSIS OF SECONDARY SAFETY ENDPOINTS

Table 11 specifies the secondary safety endpoints, including the timepoint measured, population measure, groups being compared and the measure of association between groups (where relevant).

**Table 11. Safety endpoints**

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

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

# 9 ANALYSIS OF EXPLORATORY OUTCOMES

## 9.1 ANALYSIS OF BREAKTHROUGH INFECTION ENDPOINTS

Breakthrough infections will be defined in three ways:

i) Documented infections (positive by RAT or PCR)

ii) Undocumented infections: Defined as a fold-change of ≥1.2 in spike-specific SARS-CoV-2 Wuhan IgG results between visits (from Day-28 onwards)

iii) Undocumented infections identified through N-Protein IgG

Table 12 lists the breakthrough infection endpoints, including the timepoint measured, population measure, groups being compared and the measure of association between groups.

**Table 12. Breakthrough infection endpoints**

| Breakthrough Infection Endpoint | Outcome | Timepoint[#] | Population measure | Comparison | Measure of association |
|---|---|---|---|---|---|
| i. | Breakthrough infection^ | To Day-28 visit; Month-6 visit; Month-12 visit; Month-18, Month-24, Month-30 | Incidence risk | Group A vs Group B vs Group C | Descriptive only |
| ii. | Breakthrough infection^ by time-period (<14 days, Day 14 – Day-28 visit, Day-28 visit – Month-6 visit, Month-6 visit – Month-12 visit, Month-12 visit – Month-18 visit, Month-18 visit – Month 24 visit, Month-24 visit – Month 30 visit) | | Incidence risk | Group A vs Group B vs Group C | Descriptive only |

[#]Analysis to be repeated at each analysis timepoint, for the risk and rate of breakthrough infection to that timepoint.
^Analysis to be repeated for undocumented breakthrough infections determined through Spike and N-protein IgG.

## 9.2 ESTIMAND-TO-ANALYSIS TABLES FOR BREAKTHROUGH INFECTION ENDPOINTS

**Table 13.** Generic Estimand-to-Analysis table for all breakthrough infection endpoints for incidence risk (specified in Table 12).

| **Exploratory objective (as per Protocol):** To describe the number and severity of breakthrough cases in the control group compared with the two vaccine groups (bivalent Moderna and Novavax) | |
|---|---|
| Estimand (for each trial vaccine): | Incidence risk of [OUTCOME]* to [TIMEPOINT]*, by trial vaccine in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously |
| **ESTIMAND Attributes:** | **Incorporation of Estimand Attribute in ANALYSIS:** |
| **Treatment**<br>Bivalent mRNA Moderna COVID-19 vaccine and protein-based Novavax COVID-19 vaccine | **Study arms**<br>Bivalent Moderna vaccine arm<br>Novavax vaccine arm<br>Control arm |
| Adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously | **Analysis set**<br>All randomised participants |
| **Variable**<br>SARS-CoV-2 infection (breakthrough infection) | **Outcome measure**<br>1. Breakthrough infection as determined by at least one positive SARS-CoV-2 test (PCR)^ |

<table>
<tr><td colspan="2"></td><td>2. Undocumented BTI as defined as a fold-change of ≥1.2 in spike-specific SARS-CoV-2 Wuhan IgG results between visits</td></tr>
<tr><td colspan="2">Handling of intercurrent events<br><table><tr><td>Event</td><td>Strategy[4]</td></tr><tr><td>Receipt of 5th dose (self-initiated)</td><td>Treatment Policy (interpret results in conjunction with 5th dose coverage)</td></tr></table></td><td rowspan="2">Handling of missing data<br>Active surveillance for SARS-CoV-2 is not being done. Therefore, participants without a positive SARS-CoV-2 test will be included in the analysis assuming they have not had a breakthrough infection.</td></tr>
<tr><td colspan="2">Population-level summary measure<br>Incidence risk (proportion positive)</td></tr>
<tr><td colspan="2"></td><td>Analysis approach<br>The incidence risk (a proportion) will be reported in each group. Analyses are descriptive only (no formal comparisons between arms will be made). See Dummy Table 3.<br><br>Planned figures<br>The individual trajectories of binding antibody titres (Wuhan) over time will be graphically displayed using line (spaghetti) plots, separately by group. Different colours will be used to identify individuals that have had a ≥1.2 fold-change between visits.</td></tr>
</table>

*This table is generic for all breakthrough infection endpoints for incidence risks (with varying combinations of outcomes and timepoints) specified in Table 12, as they will be analysed in the same way.
^Analysis to be repeated for undocumented breakthrough infections

### 9.3 SEQUENCING OF NASAL SWABS FROM BREAKTHROUGH INFECTION

Self-collected nasal swabs will undergo whole genome sequencing for SARS-CoV-2. The distribution of clades and lineages identified from the BTI cases will summarised using frequencies and proportions. The distribution of SARS-CoV-2 clades/lineages over time be displayed graphically using a stacked bar chart (Monthly stacked bars with frequencies, with different segments for different clades/lineages).

## 9.4 SUPPLEMENTARY AND SENSITIVITY ANALYSES

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

**Table 14. Supplementary and Sensitivity Analyses**

| | MAIN ANALYSIS (Complete Case) | | SUPPLEMENTARY ANALYSIS (for IcE Strategy) | | | SENSITIVITY ANALYSIS (for >5% missingness) |
|---|---|---|---|---|---|---|
| **Endpoints** | **Estimand** | **IcE & Strategy** | **Change to Estimand from Main Analysis** | **IcE & Strategy** | **Impact** | |
| **Primary immunological endpoint (seroresponse at Day-28)** | Geometric mean ratio (GMR) of binding antibodies (IgG ELISA – Wuhan, Omicron BA.1 and Omicron BA.4/5) 28 days post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax) in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of SARS-CoV-2 infection. | SARS-CoV-2 infection: Treatment Policy | …, irrespective of SARS-CoV-2 infection ≤ 14 days post-booster, and in a hypothetical scenario in which there were no breakthrough infections on or after Day 15. | SARS-CoV-2 infection ≤ 14 days post-booster: Treatment Policy<br><br>SARS-CoV-2 infection on or after Day 15: Hypothetical[δ] | Imagines a scenario in which breakthrough infections on or after Day 15 did not occur. | The main analysis, including all participants, will be repeated through multiple imputation (MICE) of missing outcome and covariate data. |
| **Day-28 Secondary immunological endpoints[#]** | [Geometric mean ratio in [OUTCOME] OR Difference in Means of [OUTCOME]][#] 28 days post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax), in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of SARS-CoV-2 infection. | SARS-CoV-2 infection: Treatment Policy | As above | As above | As above | |
| **Month-[6/12/18/24/30]^ Secondary immunological endpoints[#]** | [Geometric mean ratio in [OUTCOME] OR Difference in Means of [OUTCOME]][#] [6/12]^ months post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax), in | SARS-CoV-2 infection: Treatment Policy | …, irrespective of SARS-CoV-2 infection ≤ 14 days post-booster or receipt of a 5th dose (self-initiated), and in a | SARS-CoV-2 infection ≤ 14 days post-booster: | As above | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of breakthrough infections or receipt of a 5th dose (self-initiated). | Self-initiated 5th dose: Treatment Policy | hypothetical scenario in which there were no breakthrough infections on or after Day 15 | Treatment Policy<br><br>Receipt of 5th dose (self-initiated): Treatment Policy<br><br>SARS-CoV-2 infection on or after Day 15: Hypothetical$^{\delta}$ | | |
| **Month-[6/12/18/24/30]^ Secondary immunological endpoints#** | Geometric mean ratio in [OUTCOME] OR Difference in Means of [OUTCOME]]# [6/12]^ months post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax), in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of breakthrough infections or receipt of a 5th dose (self-initiated). | SARS-CoV-2 infection: Treatment Policy<br><br>Self-initiated 5th dose: Treatment Policy | …, irrespective of SARS-CoV-2 infection), and in a hypothetical scenario in which no participants received a self-initiated 5th dose. | SARS-CoV-2 infection**:** Treatment Policy<br><br>Receipt of 5th dose (self-initiated): Hypothetical$^{\delta}$ | Imagines a scenario in which no participants received a self-initiated 5th dose. | |
| **Month-[6/12/18/24/30]^ Secondary immunological endpoints#** | Geometric mean ratio in [OUTCOME] OR Difference in Means of [OUTCOME]]# [6/12]^ months post-vaccination comparing the two vaccine groups (bivalent Moderna and Novavax), in adults 18 years or older who have received their third dose of COVID-19 vaccine at least six months previously, irrespective of breakthrough infections or receipt of a 5th dose (self-initiated). | SARS-CoV-2 infection: Treatment Policy<br><br>Self-initiated 5th dose: Treatment Policy | …, irrespective of SARS-CoV-2 infection ≤ 14 days post-booster, and in a hypothetical scenario in which:<br>- there were no breakthrough infections on or after Day 15, AND;<br>-no participants received a self-initiated 5th dose. | SARS-CoV-2 infection ≤ 14 days post-booster**:** Treatment Policy<br><br>SARS-CoV-2 infection on or after Day 15: Hypothetical$^{\delta}$<br><br>Receipt of 5th dose (self- | Imagines a scenario in which:<br><br>-breakthrough infections on or after Day 15 did not occur.<br><br>AND<br><br>-no participants received a self-initiated 5th dose | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | initiated): Hypothetical[δ] | | |

[#]This row is generic for all immunological endpoints at the specified timepoint (see Table 8). This row is generic for the Month-6 and Month-12 timepoints. [δ]Under the hypothetical strategy, outcome values experienced after the specified intercurrent events will be set to missing and multiple imputation will be used to calculate the estimate including these participants. The parts of the Estimands and intercurrent event strategies that are being modified in each supplementary analysis are highlighted by blue text.

### 9.4.1 Implementation of the Hypothetical Strategy

Under the hypothetical strategy, outcome values experienced after the specified intercurrent events will be set to missing and multiple imputation will be used to calculate the estimate including these participants. Multiple imputation for analyses under the hypothetical strategy will be carried out using the same imputation procedure used to handle missing data (see Section 4.10). Imputation will be done separately by trial arm. For Month-6, Month-12, Month-18,Month-24 endpoints and Month-30 endpoints, levels of the outcome variable at previous blood draws will also be included in the imputation model.

### 9.5 SUBGROUP ANALYSES AND TESTS FOR INTERACTION

Analyses for all endpoints will be conducted amongst all strata combined. Primary analyses will combine data from participants receiving the Moderna BA.1 and Moderna BA.4/5 vaccines. Subgroup analyses stratified by the age strata (<50 and ≥50 years) will also be conducted for the immunological endpoints and breakthrough infection secondary endpoints. Subgroup analyses will also be performed by Moderna vaccine timing (Moderna BA.1 period vs Moderna BA.4/5 period) for immunological endpoints . Tests of interaction will be done by fitting a model with an interaction parameter between study arm and the age strata.

### 9.6 ANALYSIS OF SAFETY ENDPOINTS

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

In addition, a list of all adverse events will be provided by trial vaccine including the following parameters:

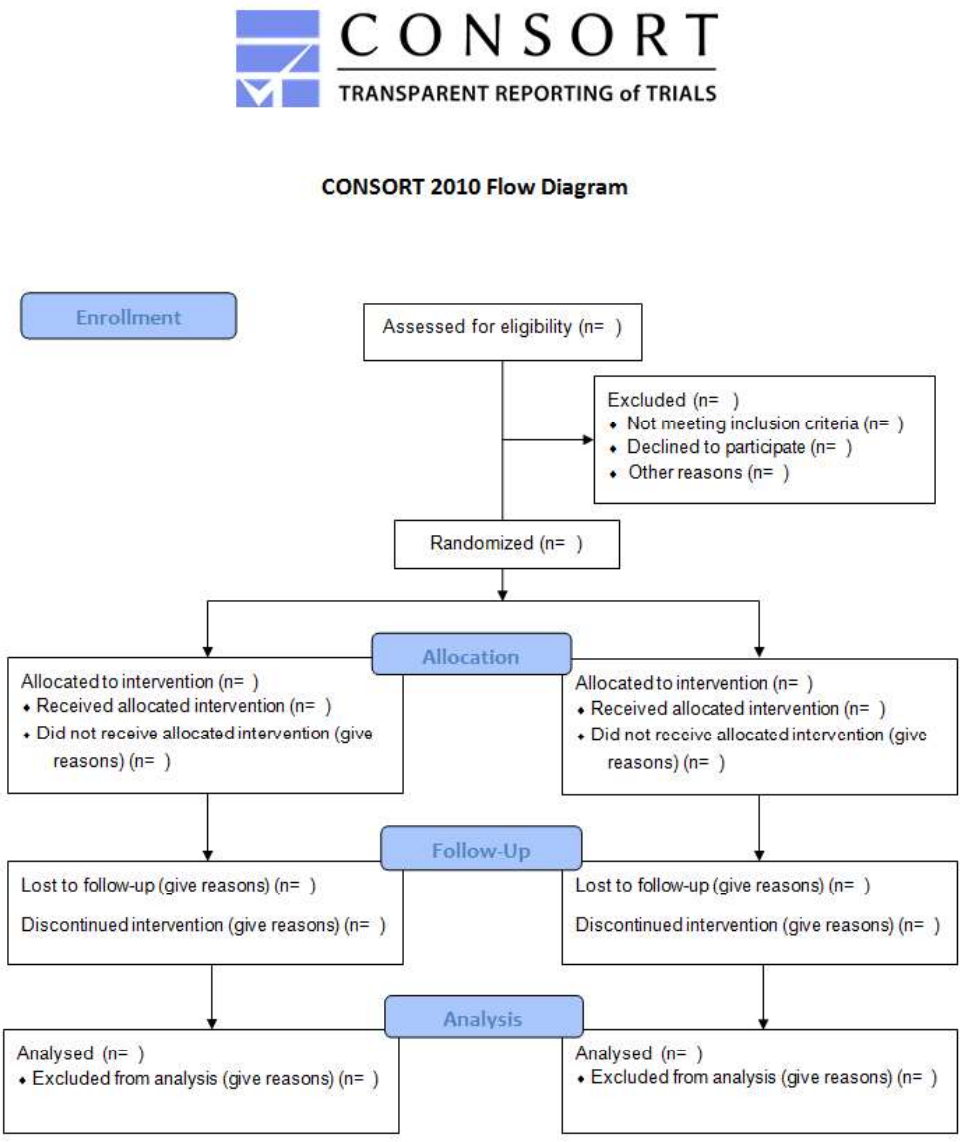
- the patient identifier
- age
- sex
- adverse event (reported term, lower-level term, and SOC)
- day of onset (from Day 0)
- duration (in days)
- severity grade
- seriousness (serious/non-serious)
- special interest (yes/no)
- expectedness (yes/no)
- action taken
- outcome (Resolved, Resolved with sequelae, Ongoing, Fatal and Unknown)
- causality assessment/relatedness *(noting 'adverse reactions' and 'serious adverse reactions')*
- concomitant medication at baseline
- concomitant medication during study (prior to event)
- concomitant medication in response to event
- comorbidities at baseline
- brief narrative (SAEs only)

## 10 PLANNED TABLES AND FIGURES

### 10.1 PLANNED TABLES AND FIGURES

| **Main** | | **Dummy Table** |
|---|---|---|
| Figure 1 | CONSORT diagram | Dummy Figure 1 |
| Table 1 | Baseline characteristics by study group | Dummy Table 1 |
| Figure 2 | Radial graph for solicited grade 3 or 4 local and systemic reactions within 7 days of boosting, inclusive, by vaccine group | Dummy Figure 2 |
| Figure 3 | Distribution of primary immunological outcome at baseline and Day-28 [and Month-6 and Month-12], by study group | Dummy Figure 3 |
| Table 2 | Immune responses at <<Day-28/Month-6/Month-12/Month-18/Month-24/Month-30>> by study group | Dummy Table 2 |
| Table 3 | Breakthrough infections by study group | Dummy Table 3 |
| **Supplement** | | |
| Table S1 | Proportion of participants who received additional COVID-19 vaccine dose during the study period | Dummy Table S 1 |
| Figure S1 | Percentage of individuals with each reaction and severity grade, for each schedule. | Dummy Figure S 1 |
| Table S2 | Frequency and outcomes of unsolicited adverse events and serious adverse events | Dummy Table S 2 |
| Figure S2 | Frequency of unsolicited adverse events to Day 28 (inclusive) by SOC and severity | Dummy Figure S 2 |
| Figure S3 | Day of unsolicited AE onset (days post-booster) to Day 28 (inclusive) by SOC | Dummy Figure S 3 |
| Table S3 | Line list of all unsolicited adverse events | - |
| Text | Summary of protocol violations | - |
| Table S4 | Clinical observations before trial vaccination | - |
| Table S5 | Concomitant medications (regular medications at baseline) | - |

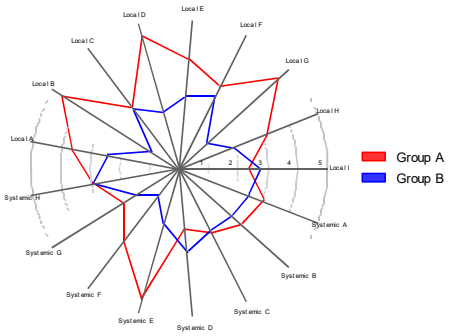
### 10.1.1 Dummy Tables and Figures – Main



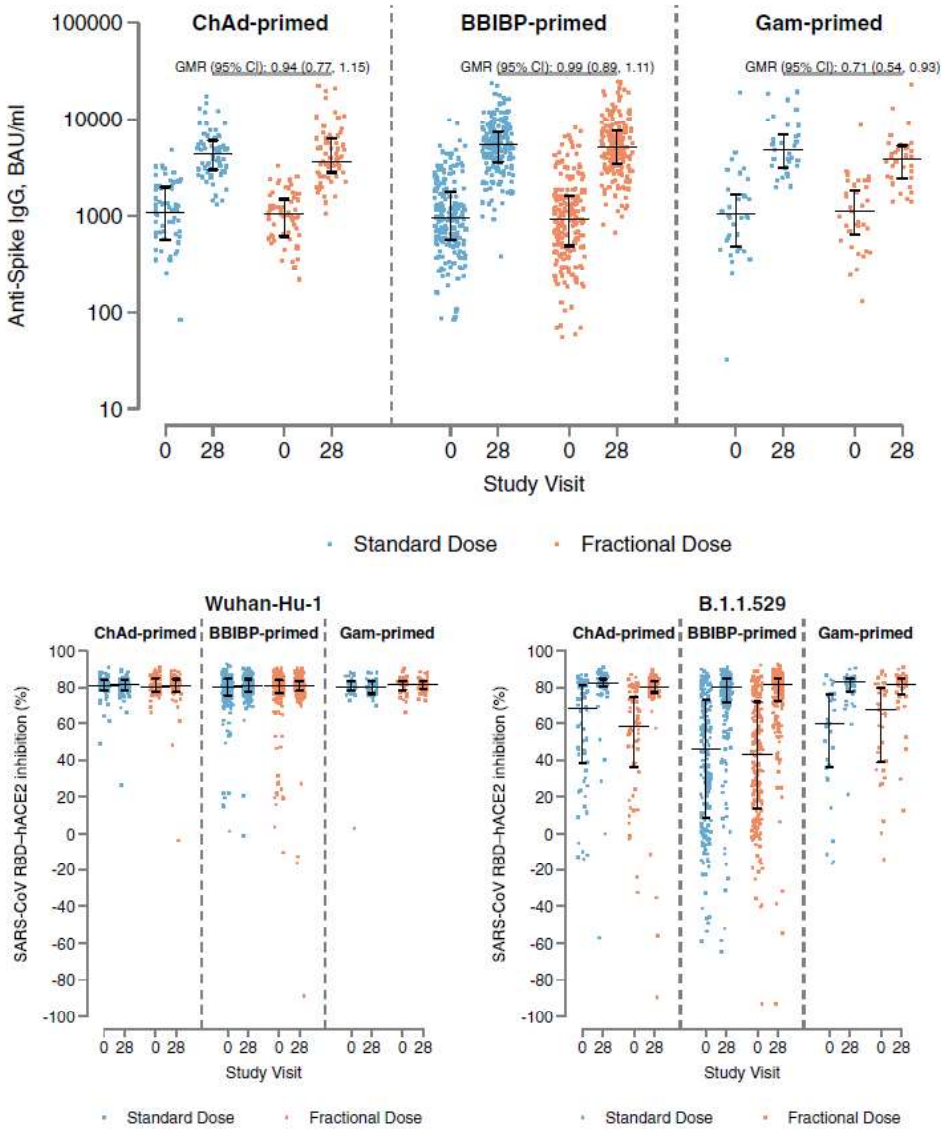

**Dummy Figure 1. CONSORT Flow Diagram**

**Dummy Table 1.** Baseline characteristics by study group

| | Total (N = n) | Moderna (N = n) | Novavax (N = n) | Control (N=n) |
|---|---|---|---|---|
| Age, years | Mean [SD] or Median {IQR}, min-max | Mean [SD] or Median {IQR}, min-max | Mean [SD] or Median {IQR}, min-max | Mean [SD] or Median {IQR}, min-max |
| Age groups, years | | | | |
| 18 – 49 years | N (%) | N (%) | N (%) | N (%) |
| ≥50 | N (%) | N (%) | N (%) | N (%) |
| Biological sex assigned at birth | | | | |
| Female | N (%) | N (%) | N (%) | N (%) |
| Male | N (%) | N (%) | N (%) | N (%) |
| BMI, $kg/m^2$ | Median {IQR} | Median {IQR} | Median {IQR} | Median {IQR} |
| Interval between 1st and 2nd dose, days | Median {IQR}, min-max | Median {IQR}, min-max | Median {IQR}, min-max | |
| Interval between 2nd and 3rd dose, days | Median {IQR}, min-max | Median {IQR}, min-max | Median {IQR}, min-max | |
| Interval between 3rd and 4th (study) dose, days | Median {IQR}, min-max | Median {IQR}, min-max | Median {IQR}, min-max | |
| Reaction to primary series | N (%) | N (%) | N (%) | |
| Highest level of medical care sought for reaction to primary series | N (%) | N (%) | N (%) | |
| No care/advice sought | N (%) | N (%) | N (%) | |
| Pharmacy | N (%) | N (%) | N (%) | |
| GP | N (%) | N (%) | N (%) | |
| Emergency Department | N (%) | N (%) | N (%) | |
| Admitted to Hospital | N (%) | N (%) | N (%) | |
| Other | N (%) | N (%) | N (%) | |
| Comorbidities | N (%) | N (%) | N (%) | N (%) |
| Diabetes mellitus | N (%) | N (%) | N (%) | N (%) |
| Gestational diabetes | N (%) | N (%) | N (%) | N (%) |
| Cardiovascular disease | N (%) | N (%) | N (%) | N (%) |
| Hypertension | N (%) | N (%) | N (%) | N (%) |
| Cancer | N (%) | N (%) | N (%) | N (%) |
| Chronic obstructive pulmonary | N (%) | N (%) | N (%) | N (%) |
| Chronic kidney disease | N (%) | N (%) | N (%) | N (%) |
| Chronic liver disease | N (%) | N (%) | N (%) | N (%) |
| Anaphylaxis (or carries an EpiPen) | N (%) | N (%) | N (%) | N (%) |
| Neurological disease (including stroke) | N (%) | N (%) | N (%) | N (%) |
| Asthma | N (%) | N (%) | N (%) | N (%) |
| Anticoagulant therapy | N (%) | N (%) | N (%) | N (%) |
| | | | | |
| Mastocytosis causing recurrent anaphylaxis | N (%) | N (%) | N (%) | N (%) |
| Cigarette user | N (%) | N (%) | N (%) | N (%) |
| Currently pregnant | N (%) | N (%) | N (%) | N (%) |




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



**Dummy Figure 3.** Distribution of primary immunological outcome. Dummy figure is from Bathmunkh et al. (2023). The graph will present data by Moderna and Novavax study groups (rather than standard and fractional dose).

**Dummy Table 2.** Immune responses at <<Day-28/Month-6/Month-12/Month-18/Month-24/Month-30>> by study group and comparison across groups. Lines to be added for additional endpoints/timepoints.

| | Moderna (N = n) | Novavax (N = n) | Control (N = n) | Moderna/ Novavax | Moderna/ Control | Novavax/ Control |
|---|---|---|---|---|---|---|
| Endpoint at timepoint x | GM (95% CI) [n=xx] | GM (95% CI) [n=xx] | GM (95% CI) [n=xx] | GMR (95% CI) | GMR (95% CI) | GMR (95% CI) |
| Endpoint at timepoint y | Median (95% CI) [n=xx] | Median (95% CI) [n=xx] | Median (95% CI) [n=xx] | Difference in medians (95% CI) | Difference in medians (95% CI) | Difference in medians (95% CI) |

GM = geometric mean, GMR = geometric mean ratio
*There will be no comparisons with the control group at Day 28

**Dummy Table 3.** Breakthrough infections by study group.

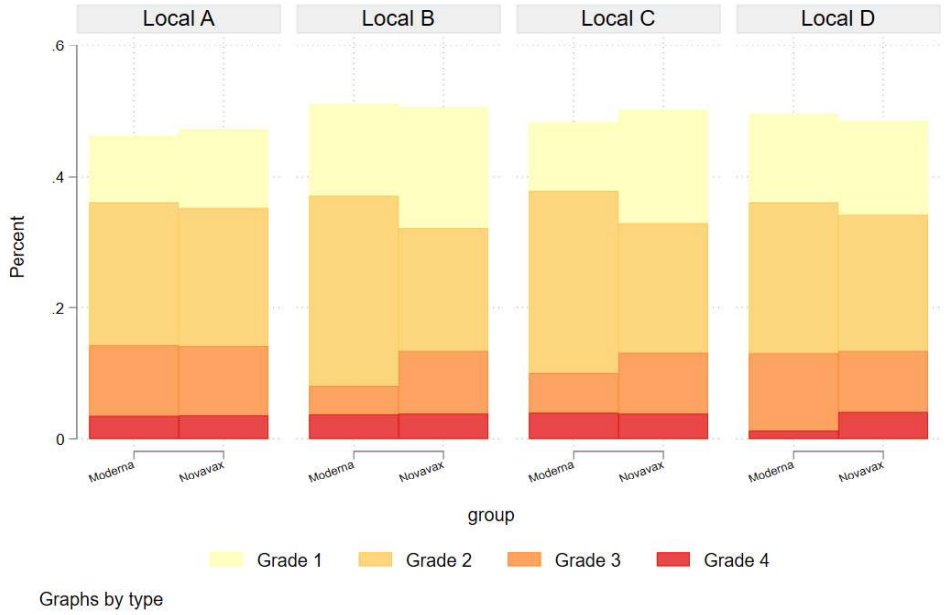
| | Moderna (N = n) | Novavax (N = n) | Control (N = n) | Total (N = n) |
|---|---|---|---|---|
| Received additional dose (Total) | N (%) | N (%) | N (%) | N (%) |
| Before Month-6 visit | N (%) | N (%) | N (%) | N (%) |
| Between 6 and 12 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 12 and 18 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 18 and 24 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 24 and 30 month visit | N (%) | N (%) | N (%) | N (%) |
| Total breakthrough blood samples collected (% of BTI) | N (%) | N (%) | N (%) | N (%) |
| Total breakthrough blood samples collected (% of BTI) | N (%) | N (%) | N (%) | N (%) |

*Table to be repeated for undocumented breakthrough infections

### 10.1.2 Dummy Tables and Figures - Supplement

**Dummy Table S 1. Numbers of participants who received an additional COVID-19 vaccine dose by study group and study period**

| | Moderna (N = n) | Novavax (N = n) | Control (N = n) | Total (N = n) |
|---|---|---|---|---|
| Received additional dose (Total) | N (%) | N (%) | N (%) | N (%) |
| Before Month-6 visit | N (%) | N (%) | N (%) | N (%) |
| Between 6 and 12 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 12 and 18 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 18 and 24 month visit | N (%) | N (%) | N (%) | N (%) |
| Between 24 and 30 month visit | N (%) | N (%) | N (%) | N (%) |

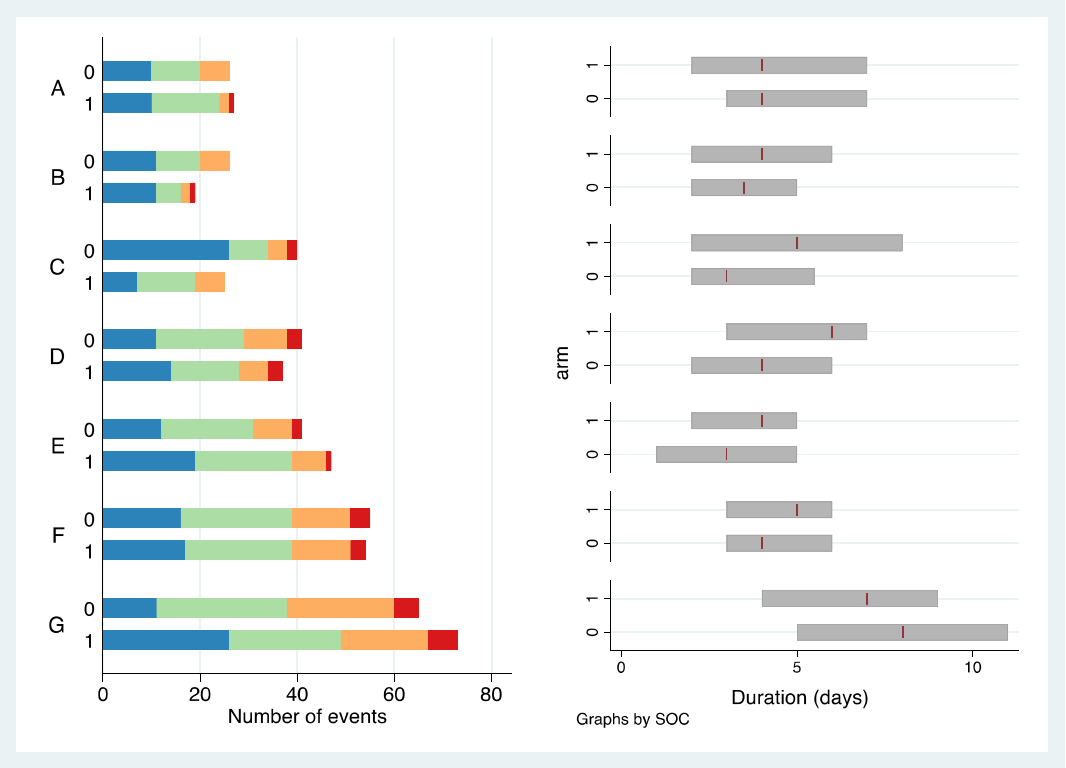



**Dummy Figure S 1.** Dummy figure to show the percentage of individuals with each reaction and severity grade, for each schedule.

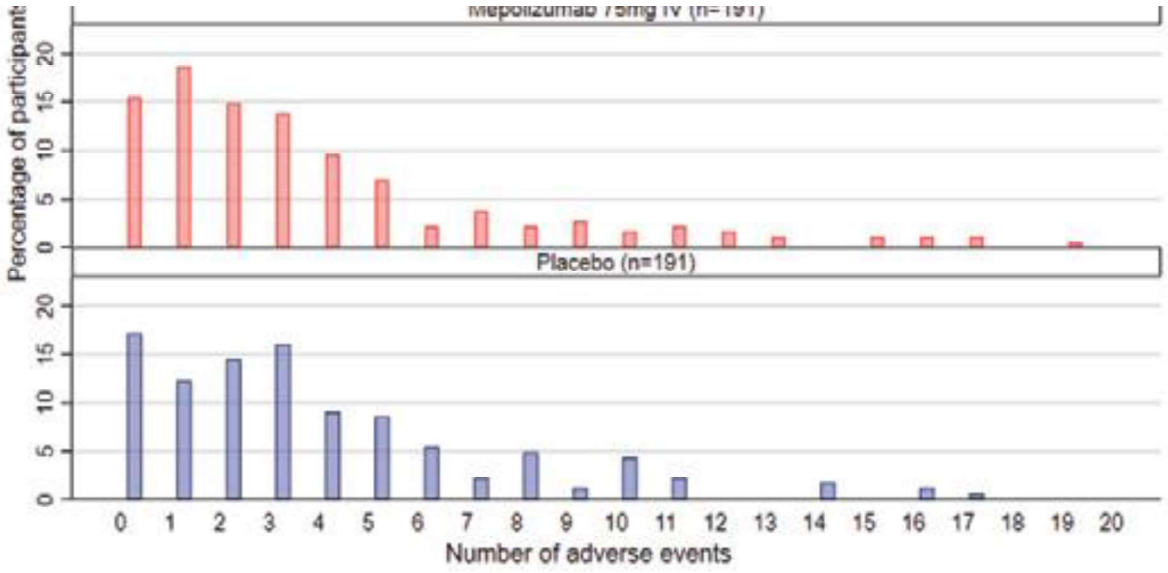
**Dummy Table S 2. Frequency and outcomes of unsolicited adverse events and serious adverse events**

| | Total (N = n) | Moderna (N = n) | Novavax (N = n) |
|---|---|---|---|
| Any AE to Day 28 (inclusive) * | N (%) | N (%) | N (%) |
| Any Grade 3 - 5 AE to Day 28 (inclusive) *^ | N (%) | N (%) | N (%) |
| AE Outcome# | | | |
| Resolved | N (%) | N (%) | N (%) |
| Resolved with sequelae | N (%) | N (%) | N (%) |
| Ongoing | N (%) | N (%) | N (%) |
| Fatal | N (%) | N (%) | N (%) |
| Unknown | N (%) | N (%) | N (%) |
| Medically attended AE to Month-3 visit (inclusive) | N (%) | N (%) | N (%) |
| Any SAE to study-end^ | | | |
| SOC A | N (%) | N (%) | N (%) |
| SOC B | N (%) | N (%) | N (%) |
| SOC C | N (%) | N (%) | N (%) |
| … for all SOCs … | N (%) | N (%) | N (%) |
| SAE Outcome# | | | |
| Resolved | N (%) | N (%) | N (%) |
| Resolved with sequelae | N (%) | N (%) | N (%) |
| Ongoing | N (%) | N (%) | N (%) |
| Fatal | N (%) | N (%) | N (%) |
| Unknown | N (%) | N (%) | N (%) |

*Unsolicited Adverse events within 28 days inclusive will be considered, rather than all adverse events before the Day-28 visit, which can occur between 28- and 35-days post-booster. ^Recurrent events in the same individual will be counted as a single event (using information from the most severe occurrence); all recurrences will be included in the line list of all adverse events. #Denominator is the total number of AEs/SAEs rather than the number of participants.




**Dummy Figure S 2.** The frequency of unsolicited adverse events to Day 28 (inclusive) by SOC, severity, and event duration. A – G are different SOCs. Colours represent event severity (Blue=Mild; Red = Severe). [Note: *This type of figure will be generated separately for each trial vaccine and presented in panels within a single figure.*]




**Dummy Figure S 3.** Onset (days post-booster) of unsolicited AE to Day 28 (inclusive) by SOC. Dummy figure is from Phillips *et al.* 2022.[7] X-axis will be the day of onset rather than the number of adverse events. Mepolizumab and Placebo correspond to Moderna and Novavax vaccine groups.

# 11 REFERENCES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4 Committee for Medicinal Products for Human Use. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. 2020.

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

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7 Phillips R, Cro S, Wheeler G, *et al.* Visualising harms in publications of randomised controlled trials: consensus and recommendations. *BMJ* 2022; : e068983.