Trials

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Bringing optimised COVID-19 vaccine schedules to immunocompromised populations: statistical elements and design

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Abstract

Bringing optimised coronavirus disease 2019 (COVID-19) vaccine schedules to immunocompromised populations (BOOST-IC) is a multi-site, adaptive platform trial designed to assess the effect of different booster vaccination schedules in the Australian immunocompromised population on the immunogenicity, safety and cross-protection against COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants. Participants from one of three immunocompromised subpopulations (people living with human immunodeficiency virus, solid organ transplants or haematological malignancies) are randomised to receive a one- or two-dose booster vaccination schedule using one of three COVID-19 vaccine brands (Pfizer, Moderna or Novavax) available in Australia. The primary endpoint is the SARS-CoV-2 anti-spike immunoglobulin G concentration at 28 days after the final dose of study vaccine and is modelled using a Bayesian hierarchical two-part model, anticipating that a significant proportion of responses may be below the limit of assay detection. We describe the structure and objectives of the BOOST-IC trial and how these are mathematically represented, modelled and reported, including specification of the estimands, statistical models and decision criteria for trial adaptations. This paper should be read in conjunction with the BOOST-IC study protocol. BOOST-IC was registered on 27 September 2022 with the Australian and New Zealand Clinical Trials Registry NCT05556720.

Keywords COVID-19, Vaccine, Immunocompromised, Adaptive trial, Statistical model, Bayesian, Immunogenicity

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Introduction

Immunocompromised populations continue to be disproportionately impacted by the coronavirus disease of 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. In these populations, there is still uncertainty around the optimal strategies for COVID-19 booster vaccination, including how vaccination impacts key elements of immunity, and how these immune responses correlate with protection against infection and disease in different populations, especially against future variants of concern (VoC) [2–5].

Platform trial designs, such as the platform trial in COVID-19 priming and boosting (PICOBOO), are being increasingly used to generate evidence for COVID-19 prevention and treatment strategies [6, 7]. Platform designs are more flexible and can be more resource efficient than conventional fixed designs because they address multiple research questions in parallel and incorporate pre-specified trial adaptations such as stopping recruitment early for superiority or futility following repeated scheduled analyses. Bayesian methods for platform designs may achieve further efficiencies through the sharing of information across multiple participant populations (e.g. immunocompromised subpopulations) and standardised procedures (e.g. timing of visits and blood samples, safety monitoring) under a single core protocol [8–10].

Bringing optimised COVID-19 vaccine schedules to immunocompromised populations (BOOST-IC) is a multi-site, adaptive platform trial designed to assess the effect of alternative booster vaccination schedules on the immunogenicity, safety and cross-protection against SARS-CoV-2 and its variants, in the Australian immunocompromised population [11] (Australian and New Zealand Clinical Trials Registry NCT05556720). We summarise the structure and objectives of the BOOST-IC trial and how these are mathematically represented, modelled and reported, including specification of the estimands, statistical models and decision criteria for trial adaptations. This paper should be read in conjunction with the BOOST-IC study protocol [11]. Given the complex statistical modelling, we intend to supplement the study protocol following a similar approach for the PICOBOO trial [12], employing much of the same structure and notation.

We begin by briefly describing the trial structure before specifying the trial subpopulations, randomisation methods and estimands. The Bayesian modelling approach follows [13, 14], along with a description of the planned trial adaptations and the pre-specified decision criteria evaluated at each scheduled analysis [15]. The estimands (ICH E9 (R1)) define the vaccine effects to be quantified, incorporating the target populations, endpoints, statistical methods and models, population level estimators and how to account for intercurrent events [16]. We conclude with a summary of the design at trial commencement and a discussion on how the BOOST-IC trial compares to other innovative contemporaneous designs that can be used to inform vaccine policy.

Trial structure

The BOOST-IC adaptive platform trial is designed to assess the immunogenicity and safety of one- or two-dose booster vaccination schedules across three COVID-19 vaccine brands in immunocompromised populations. Strata are defined by immunocompromised subpopulation and baseline SARS-CoV-2 anti-spike immunoglobulin G (IgG) antibody serostatus. The trial has the capacity to accommodate additional strata, vaccine brands, vaccine brand subtypes (vaccine subtypes produced by the same manufacturer, e.g. bivalent BA.4/5, XBB.1.5) as both novel vaccines and policy evolves over time in response to emerging VoC. We define, in detail, the notation for participants, strata, interventions, trial vaccine dose numbers, covariates and time epochs in the following sections.

Participants

Let N be the number of participants included in a given analysis where participants are denoted by $i \in \boldsymbol{I} = \{1, 2, \ldots, N\}$.

Strata: immunocompromised subpopulation and baseline serostatus

Mutually exclusive immunocompromised subpopulations are denoted by $j \in \boldsymbol{J} = \{\text{HIV}, \text{SOT}, \text{HM}\}$ and SARS-CoV-2 anti-spike IgG antibody serostatus at enrolment (hereafter known as baseline serostatus) is denoted by $l \in \boldsymbol{L} = \{\text{Undetectable}, \text{Detectable}\}$. Here, HIV, SOT and HM represent people living with human immunodeficiency virus, solid organ transplants and haematological malignancies, respectively. Participants who are eligible for multiple subpopulations are assigned to the single subpopulation judged to be the most immunocompromising by the treating clinician. Strata are defined as mutually exclusive groups based on the combination of the participant's immunocompromised subpopulation and baseline serostatus. BOOST-IC has the capacity to include additional strata as part of the design as the trial progresses.

Interventions

Separate vaccine brands are denoted by $v \in \{1, 2, \ldots, V\}$. Vaccine brand v has subtypes (vaccine subtypes produced by the same manufacturer) $s_v \in \{1, 2, \ldots, S_v\}$, where S_v is

the total number of subtypes for vaccine brand v. Separate vaccine interventions are denoted:

$$k \in \boldsymbol{K} = \{(v, s_v)\} = \{(1,1),(1,2),\ldots,(1,S_1),(2,1),(2,2),\ldots,(2,S_2),\ldots,(V,1),(V,2),\ldots,(V,S_V)\}$$

Acknowledging that vaccine subtypes vary over time and, within the Australian setting, brand availability is often restricted to the most recent vaccine subtype, there will only be up to three vaccine interventions allocated in the trial at any one time, where each allocation is for the most recently released brand subtype (i.e. allocations to BA.1 vaccine cease when the next VoC vaccine, BA.4/5, becomes available). This labelling will also easily accommodate new interventions should these options expand over time, whether these are vaccine brands or vaccine brand subtypes.

Trial vaccine dose number

Participants are randomised with equal allocation probabilities to either a one- or two-dose trial vaccine schedule. The trial vaccine dose numbers are denoted $t \in \boldsymbol{T}_i \subseteq \boldsymbol{T} = \{1,2\}$. Here, $\boldsymbol{T}_i$ refers to the set of available trial dosing occasions for participant i. We make this distinction clear as participants will receive trial doses according to their randomised schedule (one or two doses) and consequently provide varying numbers of observations. Note that participants allocated to a two-dose schedule will provide an additional blood sample at approximately 28 days following randomisation (i.e. following the first vaccine occasion) to align with the participants allocated to a one-dose schedule. This will provide additional data to inform the estimands at 28 days.

Covariates

Participant i's covariates are denoted $\boldsymbol{x}_i = \{x_{i1}, x_{i2}, \ldots, x_{iP}\}$, and are governed by P model parameters. The covariates may include standardised baseline outcome, previous COVID-19 infection (defined below), number of previous (non-trial) SARS-CoV-2 vaccine doses, site and sex. Continuous covariates are standardised within stratum and the reference value for categorical covariates is set to the most frequently observed value. The covariates included in the model may differ for each estimand.

Previous COVID-19 infection

The covariate *previous COVID-19 infection* is derived using participant reported previous SARS-CoV-2 infection in combination with their baseline anti-nucleocapsid antibodies test result, where detection indicates previous infection. The absence of any evidence of detection (self reports or nucleocapsid test results) is assumed to be no previous infection. The details for this derivation are in Table 1.

Time epochs

We introduce time epochs to address potential concerns regarding the impact of time on a multi-year trial (e.g. evolution of the circulating SARS-CoV-2 variants, prevalence of COVID-19 infection, prevalence of seasonal infectious diseases). We denote participant i's time epoch relative to the data cutoff date as $\boldsymbol{z}_i = \{z_{i1}, z_{i2}, \ldots, z_{iQ}\}$, where there are Q epochs. At each scheduled analysis, epochs will start at the date of data cut-off and be counted backwards using 6 month periods until the time of trial commencement with the most recent epoch as the reference level. Epochs will be modelled using the 'Bayesian time machine' approach demonstrated by Saville et al. [12, 17–19].

Analysis sets

We define distinct but potentially overlapping analysis sets (trial populations) in Table 2 in order to precisely define the estimands.

Randomisation

Enrolled participants will be allocated at random to one of the available interventions and to either a one- or two-dose schedule with equal allocation probabilities (i.e. without blocking). Randomisation will be conducted centrally using a computer-generated random allocation algorithm and will be stratified by immunocompromised subpopulation. New vaccines will replace existing interventions as the trial progresses and available vaccines reflect the circulating variants.

Table 1 Derivation of previous COVID-19 infection covariate

Participant reported previous SARS-CoV-2 infection	Baseline anti-nucleocapsid antibodies test result	Derived variable
No	Negative	No
	Positive	Yes
	Missing	No
Yes	Negative	Yes
	Positive	Yes
	Missing	Yes
Missing	Negative	No
	Positive	Yes
	Missing	No

Table 2 Summary of analysis sets

Analysis set	Abbreviation	Description
Modified intention-to-treat	MI	All participants who were randomised to an intervention, provided a blood sample within the appropriate estimand window and do not have evidence of receiving a non-trial SARS-CoV-2 vaccine dose between randomisation and the time of endpoint collection. Participants will be analysed according to their assigned intervention irrespective of withdrawal, treatment compliance or other protocol deviations.
Modified intention-to-treat subgroup	MI-S	Subset of MI without evidence of a SARS-CoV-2 infection or receiving antibody therapy between randomisation and the time of endpoint collection. Evidence of SARS-CoV-2 infection after randomisation may include a rapid antigen test or polymerase chain reaction confirmed self-reported infection or a positive anti-nucleocapsid antibodies test for participants with a negative anti-nucleocapsid antibodies test at baseline.
Immunological subset	IS	Subset of MI who were sequentially enrolled at selected sites to provide blood samples for additional detailed laboratory analysis.
Immunological subset subgroup	IS-S	Subset of MI-S who were sequentially enrolled at selected sites to provide blood samples for additional detailed laboratory analysis.
Safety population	SP	All participants who were randomised to, and received, an intervention. Participants will be analysed according to the intervention received, irrespective of withdrawal or other protocol deviations. Participants who do not receive a vaccine are excluded, whereas trial-ineligible participants who are incorrectly randomised and received an intervention are included.

Statistical modelling

Bayesian statistical methods allow for the incorporation of prior knowledge of intervention effects (via a prior distribution) with the observed data to produce an updated state of knowledge (a posterior distribution) [20]. The BOOST-IC adaptive trial also employs Bayesian hierarchical methods in order to efficiently share information, accrued from observed data and prior knowledge, between estimates for trial vaccine dose numbers, immunocompromised subpopulations and interventions. We detail the estimands and Bayesian models, including the prior distributions for the model parameters, in the following sections.

Estimands

The estimands are summarised in Table 3 with further detail provided in the study protocol [11]. Details on how intercurrent events will be handled for each estimand are provided in supplementary material. As the trial progresses, new and emerging laboratory tests and procedures may supersede those currently stated and existing

Table 3 Summary of trial estimands

ID	Analysis Set	Outcome	Time (window) in days[a]
01	MI-S	SARS-CoV-2 anti-spike IgG concentration	28 (21–35)
02-03	MI	SARS-CoV-2 anti-spike IgG concentration	180 (150–210) and 365 (335–395)
04	MI-S	SARS-CoV-2 anti-spike IgG serostatus	28 (21–35)
05-06	MI	SARS-CoV-2 anti-spike IgG serostatus	180 (150–210) and 365 (335–395)
07	MI-S	SARS-CoV-2 predominant circulating variant[b] anti-spike IgG concentration	28 (21–35)
08-09	MI	SARS-CoV-2 predominant circulating variant anti-spike IgG concentration	180 (150–210) and 365 (335–395)
10	IS-S	Ancestral SARS-CoV-2 neutralising antibodies response[c]	28 (21–35)
11-12	IS	Ancestral SARS-CoV-2 neutralising antibodies response	180 (150–210) and 365 (335–395)
13	IS-S	Magnitude of SARS-CoV-2 specific T-cells	28 (21–35)
14-15	IS	Magnitude of SARS-CoV-2 specific T-cells	180 (150–210) and 365 (335–395)
16	IS-S	Number of effector cytokines of SARS-CoV-2-specific T-cells	28 (21–35)
17-18	IS	Number of effector cytokines of SARS-CoV-2-specific T-cells	180 (150–210) and 365 (335–395)
19	SP	Hospitalisation resulting from an adverse event	Up to 28 (1–28)

[a] Days are counted from each trial vaccine dosing occasion for estimands 01, 04, 07, 10, 13, 16 and 19, and from final trial vaccine dosing occasion for estimands 02–03, 05–06, 08–09, 11–12, 14–15 and 17–18

[b] The predominant circulating variant(s) will be determined independently at each scheduled analysis and may vary over the course of the trial

[c] Defined separately for participants with and without a detectable baseline neutralising antibody titre; a fourfold rise in neutralising antibody titre for those with detectable titres at baseline and any detectable neutralising antibody titre for those without

tests may be removed if they are deemed unreliable or uninformative.

Descriptive statistics for demographic variables and safety outcomes

The progress of all participants through the trial phases will be summarised using a CONSORT flow diagram. Demographic data summarised by stratum, intervention and trial vaccine dose number will be presented for each analysis set. The demographic variables will include, but may not be restricted to, age, sex, ethnicity and number of previous (non-trial) SARS-CoV-2 vaccine doses. Continuous variables will be summarised by median and interquartile range and categorical variables will be summarised by frequency and percentage. Safety reporting will include tabulated and line listed summaries of solicited reactogenicity data on days 1–7 (collected via diary cards), solicited adverse events of special interest and serious adverse events.

Descriptive statistics for immunogenicity outcomes

Descriptive statistics including the geometric mean and mean and standard deviation on the data scale, summarised by stratum, intervention and trial vaccine dose number will be presented alongside each corresponding planned analysis. All descriptive statistics will be unadjusted (i.e. not modelled).

Deviations from the protocol

All deviations from the protocol, including missing visits and non-trial COVID-19 vaccines received, will be summarised by stratum, intervention and trial vaccine dose number.

Missing data

Missing outcome data will be assumed to be missing at random and excluded from analyses (i.e. a complete case strategy at each timepoint). Calender time (epoch), site and sex covariates are critical data (i.e. non-missing for all participants). Missing baseline immunological data will be set to the respective stratum standardised mean (i.e. zero).

Undetectable concentrations for baseline immune outcomes

Undetectable concentrations for baseline immunological data will be replaced with the midpoint value between zero and the limit of detection for each assay. The limit of detection for each assay will be documented in each report.

Binary outcome model

Estimands 04, 05–06, 10, 11–12 and 19 in Table 3 will be analysed using the following Bernoulli model with logit-link function for the binary outcomes denoted $o_{ijklt} \in \{0,1\}$ for participant i receiving trial vaccine dose t, allocated to intervention k in immunocompromised subpopulation j with baseline serostatus l:

$$o_{ijklt} \sim \text{Bernoulli}\left(\text{logit}^{-1}\left(a_i + \pi_{jklt} + \sum_{p=1}^{P} x_{ip}\beta_{kp} + \sum_{q=1}^{Q} z_{iq}\eta_q\right)\right) \quad \forall i \in \boldsymbol{I}, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T} \tag{1}$$

For estimands 04, 10 and 19 (day 28 outcomes) there is a participant level intercept denoted a_i as participants allocated to the two-dose schedule may provide more than one outcome ($a_i = 0$ for estimands 05–06 and 11–12). The log odds of the outcome for a participant receiving trial vaccine dose t, allocated to intervention k, in immunocompromised subpopulation j with baseline serostatus l is π_{jklt}, when the covariates are at their reference level and it is the most recent epoch. The additive effect of covariate p for a participant allocated to intervention k is denoted β_{kp} and the parameter for the effect of the q^{th} epoch is η_q (where η_1 is the most recent epoch, η_2 the previous epoch, etc., counting backwards in calendar time). The prior distributions for the parameters in (1), excluding the time epoch parameters, are:

$$a_i \sim \text{N}(0,1) \quad \forall i \in \boldsymbol{I} \tag{2}$$

$$\pi_{jklt} \sim \text{N}(0,2^2) \quad \forall j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T} \tag{3}$$

$$\beta_{kp} \sim \text{N}(0,1) \quad \forall k \in \boldsymbol{K}, p \in \{1,2,\ldots,P\} \tag{4}$$

We implement a first-order dynamic model (Bayesian time machine) for the time epoch parameters to adjust for temporal drift, with the most recent epoch η_1 as the reference and the prior distributions given by:

$$\eta_1 = 0 \tag{5}$$

$$\eta_q \sim \text{N}(\eta_{q-1}, \phi_q^2) \quad \forall q \in \{2,3,\ldots,Q\} \tag{6}$$

$$\phi_q \sim \text{IG}(3,1) \quad \forall q \in \{2,3,\ldots,Q\} \tag{7}$$

Two-part model

Estimands 01, 02–03, 07 and 08–09 in Table 3 will be analysed using a two-part model as it is anticipated that a significant proportion of the SARS-CoV-2 anti-spike IgG concentrations may be below the limit of assay

detection for some subpopulations. For participant i receiving trial vaccine dose t, allocated to intervention k in immunocompromised subpopulation j with baseline serostatus l, we denote $o_{ijklt} \in \{0, 1\}$ as an indicator variable for the corresponding concentration outcome being above the assay limit of detection (i.e. a detectable response). The binary outcome o_{ijklt} is modelled using the Bernoulli model and prior distributions described in the previous section (1)–(7). Note that the participant level intercept, a_i, will have the prior distribution defined in (2) for estimands 01 and 07 and be set to zero for estimands 02–03 and 08–09.

Then, *conditional* upon a detectable response as defined above, the corresponding observed $\log_{10}$ transformed concentration outcome is denoted $Y_{ijklt} \in \mathbb{R}$ and is modelled using the following Gaussian model:

$$Y_{ijklt}|o_{ijklt} = 1, o_{ijklt'} = 0 \sim \mathrm{N}\left(\theta_{jklt} + \sum_{p=1}^{P} x_{ip}\gamma_{kp} + \sum_{q=1}^{Q} z_{iq}\omega_q, \sigma_l^2\right)$$
$$\forall i \in \boldsymbol{I}, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T}, t' = \{t' \in \boldsymbol{T} | t' \neq t\} \tag{8}$$

$$\begin{pmatrix} Y_{ijkl1} \\ Y_{ijkl2} \end{pmatrix} | o_{ijkl1} = o_{ijkl2} = 1 \sim \mathrm{N}\left(\begin{pmatrix} \theta_{jkl1} + \sum_{p=1}^{P} x_{ip}\gamma_{kp} + \sum_{q=1}^{Q} z_{iq}\omega_q \\ \theta_{jkl2} + \sum_{p=1}^{P} x_{ip}\gamma_{kp} + \sum_{q=1}^{Q} z_{iq}\omega_q \end{pmatrix}, \boldsymbol{\Sigma}_l\right)$$
$$\forall i \in \boldsymbol{I}, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L} \tag{9}$$

Note that (8) and (9) will be used for estimands 01 and 07 as participants allocated to the two-dose schedule may provide more than one outcome, while only (8) will be used for estimands 02–03 and 08–09. The mean $\log_{10}$ concentration outcome, *conditional* on a detectable response, for a participant receiving trial vaccine dose t, allocated to intervention k, in immunocompromised subpopulation j with baseline serostatus l is θ_{jklt}, when the covariates are at their reference level and it is the most recent epoch. The additive effect of covariate p for a participant allocated to intervention k is denoted γ_{kp}, the parameter for the effect of the q^{th} epoch is ω_q (where ω_1 is the most recent epoch, ω_2 the previous epoch, etc., counting backwards in calendar time) and the baseline serostatus specific covariance matrix is $\boldsymbol{\Sigma}_l = \begin{pmatrix} \sigma_l^2 & r_l\sigma_l^2 \\ r_l\sigma_l^2 & \sigma_l^2 \end{pmatrix}$.

A hierarchical structure is imposed on the prior distributions for θ_{jklt} as it is anticipated that responses may be mutually informative across immunocompromised subpopulations, interventions and trial vaccine dose numbers (i.e. within baseline serostatus levels). However, the following prior distributions have been chosen to ensure that the level of information sharing is data driven:

$$\theta_{jklt} \sim \mathrm{N}(\mu_{\text{undet}}, \tau_{\text{undet}}^2) \quad \forall j \in \boldsymbol{J}, k \in \boldsymbol{K}, l = \text{Undetectable}, t \in \boldsymbol{T} \tag{10}$$

$$\theta_{jklt} \sim \mathrm{N}(\mu_{\text{det}}, \tau_{\text{det}}^2) \quad \forall j \in \boldsymbol{J}, k \in \boldsymbol{K}, l = \text{Detectable}, t \in \boldsymbol{T} \tag{11}$$

The priors on the mean $\log_{10}$ concentration parameters, μ_{det} and μ_{undet}, are based on data from the COV-BOOST trial publication [21] with the values for the respective hyperprior distributions informed by the mean and standard deviation $\log_{10}$ concentrations after a two-dose (priming) schedule with ChAdOx1 nCov-19 (Oxford-AstraZeneca, $\log_{10}(801)$) and after a three-dose (booster) schedule with ChAdOx1 nCov-19 ($\log_{10}(2457)$), respectively, with standard deviations on $\log_{10}$ scale of 0.3 so that the priors are weakly informative. The hyperprior distributions are:

$$\mu_{\text{undet}} \sim \mathrm{N}\left(\log_{10}(801), 0.3^2\right) \tag{12}$$

$$\mu_{\text{det}} \sim \mathrm{N}\left(\log_{10}(2457), 0.3^2\right) \tag{13}$$

$$\tau_{\text{undet}} \sim \mathrm{IG}(3, 1) \tag{14}$$

$$\tau_{\text{det}} \sim \mathrm{IG}(3, 1) \tag{15}$$

The priors on the standard deviation terms τ_{undet} and τ_{det} place the mode of the standard deviations around 0.25 with a weight of 2.3 (i.e. regularising and weakly informative with low density mass close to zero, thus information sharing will be data driven). Note that these prior means and standard deviations are specific for the analysis of estimand 01 and may vary for the analyses of other the other estimands, which will be pre-specified in statistical analysis plan.

Using a similar approach to the Bernoulli model described in the previous section, the priors for the covariate parameters and time epoch parameters are:

$$\gamma_{kp} \sim \mathrm{N}(0, 1) \quad \forall k \in \boldsymbol{K}, p \in \{1, 2, \ldots, P\} \tag{16}$$

$$\omega_1 = 0 \tag{17}$$

$$\omega_q \sim \mathrm{N}(\omega_{q-1}, \psi_q^2) \quad \forall q \in \{2, 3, \ldots, Q\} \tag{18}$$

$$\psi_q \sim \mathrm{IG}(3, 1) \quad \forall q \in \{2, 3, \ldots, Q\} \tag{19}$$

A regularising prior structure is defined for the *decomposed* covariance matrix $\boldsymbol{\Sigma}_l$, where $\boldsymbol{Q}_l$ contains the standard deviation parameters σ_l and $\boldsymbol{R}_l$ contains the correlation parameters r_l. The exponential prior assumes that larger values of the standard deviation parameters are increasingly unlikely. The Lewandowski-Kurowicka-Joe (LKJ) prior distribution is specified for the correlation matrices, where $\eta > 1$ favours smaller correlations.

$$\boldsymbol{\Sigma}_l = \boldsymbol{Q}_l \boldsymbol{R}_l \boldsymbol{Q}_l \quad \forall l \in \boldsymbol{L} \tag{20}$$

$$\boldsymbol{Q}_l = \begin{pmatrix} \sigma_l & 0 \\ 0 & \sigma_l \end{pmatrix} \quad \forall l \in \boldsymbol{L} \tag{21}$$

$$\boldsymbol{R}_l = \begin{pmatrix} 1 & r_l \\ r_l & 1 \end{pmatrix} \quad \forall l \in \boldsymbol{L} \tag{22}$$

$$\sigma_l \sim \text{Exponential}(0.5) \quad \forall l \in \boldsymbol{L} \tag{23}$$

$$\boldsymbol{R}_l \sim \text{LKJcorr}(2) \quad \forall l \in \boldsymbol{L} \tag{24}$$

Count outcome model

Estimands 13, 14–15, 16 and 17–18 in Table 3 will be analysed using the following Poisson model with log-link function for the count outcomes denoted $Y_{ijklt} \in \mathbb{Z}^+$ for participant i receiving trial vaccine dose t, allocated to intervention k in immunocompromised subpopulation j with baseline serostatus l:

$$Y_{ijklt} \sim \text{Poisson}\left(\log^{-1}\left(a_i + \lambda_{jklt} + \sum_{p=1}^{P} x_{ip}\beta_{kp} + \sum_{q=1}^{Q} z_{iq}\eta_q\right)\right) \tag{25}$$
$$\forall i \in \boldsymbol{I}, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T}$$

For estimands 13 and 16, there is a participant level intercept denoted a_i as participants allocated to the two-dose schedule may provide more than one outcome ($a_i = 0$ for estimands 14–15 and 17–18). The mean rate (on the log scale) of the outcome for a participant receiving trial vaccine dose t, allocated to intervention k, in immunocompromised subpopulation j with baseline serostatus l is λ_{jklt}, when the covariates are at their reference level and it is the most recent epoch. The additive effect of covariate p for a participant allocated to intervention k is denoted β_{kp} and the parameter for the effect of the q^{th} epoch is η_q (where η_1 is the most recent epoch, η_2 the previous epoch, etc., counting backwards in calendar time).

The prior distributions for the participant level intercepts, covariate parameters and time epoch parameters are the same as for the binary outcome model: (2) and (4)-(7). The prior distributions for the (log) mean rate parameters in (25) are:

$$\lambda_{jklt} \sim \text{N}(\log(500), 1) \quad \forall j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T} \tag{26}$$

The Poisson regression model may be replaced with a negative binomial regression model if over-dispersion is detected.

Planned exploratory subgroup analysis

A planned exploratory subgroup analysis for estimand 01 will be conducted to address the heterogeneity inherent within each of the prespecified immunocompromised subpopulations. Note that this is the only planned subgroup analysis and it is exploratory (i.e. hypothesis generating). In this analysis, we introduce subgroups denoted s_j as follows:

$$s_{\text{HIV}} \in \boldsymbol{S}_{\text{HIV}} = \{< 250 \text{ CD lymphocyte count}, \geq 250 \text{ CD lymphocyte count}\}$$
$$s_{\text{SOT}} \in \boldsymbol{S}_{\text{SOT}} = \{\text{Lung, Heart, Renal, Liver}\}$$
$$s_{\text{HM}} \in \boldsymbol{S}_{\text{HM}} = \{\text{Chronic lymphocytic leukemia, Myeloma, Lymphoma}\}$$

Note that participants may only belong to one subgroup within each immunocompromised subpopulation. Solid organ transplant recipients will be allocated to the subgroup representing their transplantation. Where multiple transplants have been received, participants will be classified to a single group based on the highest rank: 1st Lung, 2nd Heart, 3rd Renal and 4th Liver (i.e. if a participant has both a heart transplant and liver transplant then they will allocated to the heart transplant subgroup).

We replace o_{ijklt} and Y_{ijklt} with o_{is_jklt} and Y_{is_jklt}, respectively from the two-part model (i.e. the observations are denoted at the subgroup level instead of the immunocompromised subpopulation level). The likelihood components of the model keep their form with the additional replacement of the parameters π_{jklt} and θ_{jklt} with π_{s_jklt} and θ_{s_jklt}, respectively (i.e. we estimate the log odds of a detectable response and the mean $\log_{10}$ SARS-CoV-2 anti-spike IgG concentration *conditional* on a detectable response at the subgroup level instead of the immunocompromised subpopulation level). The other model parameters (a_i, β_{kp}, η_q, γ_{kp}, ω_q, σ_l and r_l), and their respective prior distributions, remain unchanged.

The prior distribution for the modified parameters for the binary component of the model are:

$$\pi_{s_jklt} \sim \text{N}(0, 2^2) \quad \forall s_j \in \boldsymbol{S}_j, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T} \tag{27}$$

The prior distributions for the continuous component of the model are hierarchical and share information first within immunocompromised subpopulation levels and then within baseline serostatus levels. The first level priors are:

$$\theta_{s_jklt} \sim \text{N}(\mu_{j,\text{undet}}, \tau^2_{j,\text{undet}}) \quad \forall s_j \in \boldsymbol{S}_j, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l = \text{Undetectable}, t \in \boldsymbol{T} \tag{28}$$

$$\theta_{s_jklt} \sim \text{N}(\mu_{j,\text{det}}, \tau^2_{j,\text{det}}) \quad \forall s_j \in \boldsymbol{S}_j, j \in \boldsymbol{J}, k \in \boldsymbol{K}, l = \text{Detectable}, t \in \boldsymbol{T} \tag{29}$$

The second level priors are:

$$\mu_{j,\text{undet}} \sim \text{N}(\mu_{\text{undet}}, \tau_{\text{undet}}) \tag{30}$$

$$\mu_{j,\text{det}} \sim \text{N}(\mu_{\text{det}}, \tau_{\text{det}}) \quad (31)$$

$$\tau_{j,\text{undet}} \sim \text{IG}(3, 1) \quad (32)$$

$$\tau_{j,\text{det}} \sim \text{IG}(3, 1) \quad (33)$$

The remaining parameters (μ_{undet}, τ_{undet}, μ_{det} and τ_{det}) have the same prior distributions as the corresponding parameters in the two part model (12)-(15). Note that the planned exploratory analysis will only be conducted once the trial has concluded.

Computational methods

All statistical models will be programmed in the probabilistic programming language Stan [22]. To interface with Stan, we use the cmdstanr package [23] within the R statistical programming environment v4.2.2 [24]. Posterior distributions will be estimated using the No-U-Turn Sampler (NUTS), which is a Markov-chain Monte Carlo (MCMC) algorithm and extends the Hamiltonian Monte Carlo (HMC) method. Each analysis will incorporate eight MCMC chains, run in parallel, with warm-up and sampling phases each running for 1000 iterations. Sampling diagnostics including trace plots, effective sample sizes and divergent transitions will be monitored and assessed to determine algorithm convergence. As appropriate, the team may adjust the sampling specifications accordingly and document this in any arising publications and reports.

Discretion is made for analyses to vary from the detail presented here in order to address model issues. For example, if some model parameters are uninformed due to no participants within a specific category or stratum then the model may be reparameterised or those parameters may not be reported. Furthermore, in consultation with the Data Safety Monitoring Committee (DSMC), the analytic team may recommend against conducting a prespecified analysis if there is insufficient data to produce meaningful results.

Quantities of interest, decision criteria and scheduled analyses

The primary quantities of interest in the BOOST-IC trial are the mean $\log_{10}$ SARS-CoV-2 anti-spike IgG concentration measured ~28 days after each trial vaccine dose for each immunocompromised subpopulation j, intervention k, baseline serostatus l and trial vaccine dose t, *conditional* on a detectable response. These quantities will be derived from estimand 01 (Table 3) using the two-part model. Model parameter θ_{jklt} posterior distributions will be employed to inform trial adaptation decisions and report to the DSMC, in addition to quantifying population-level intervention effects in any trial publications.

Intervention comparisons

At trial conclusion we will conduct a series of prespecified intervention comparisons via the quantity of interest θ_{jklt}. The intervention comparisons will be conducted within each immunocompromised subpopulation j and baseline serostatus level l. The comparisons are structured as follows:

1 Within each immunocompromised subpopulation j, intervention k and baseline serostatus level l, compare the mean $\log_{10}$ SARS-CoV-2 anti-spike IgG concentration, conditional on a detectable response, *between one and two trial vaccine doses* (t), where $P_{jkl} = \text{Prob}(\theta_{jkl2} > \theta_{jkl1})$.

   (a) If $P_{jkl} > 0.9$ then declare the two dose strategy superior to the one dose strategy for this stratum-intervention combination and select the two dose strategy for step 2.
   (b) Otherwise, select the one dose strategy for this stratum-intervention combination for step 2.
   (c) The selected dosing strategy is denoted t^* in step 2.

2 Within each immunocompromised subpopulation j and baseline serostatus level l, compare the mean $\log_{10}$ SARS-CoV-2 anti-spike IgG concentration, conditional on a detectable response, *between each intervention* (k) with the selected dosing strategies (t^*) from step 1. For the comparison between intervention k and k' compute $P_{jkk'l} = \text{Prob}(\theta_{jklt^*} > \theta_{jk'lt^*})$.

   (a) If $P_{jkk'l} > 0.9$ then declare intervention k superior to intervention k' for this stratum.
   (b) If $P_{jkk'l} < 0.1$ then declare intervention k' superior to intervention k for this stratum.
   (c) Otherwise, there is insufficient evidence to declare either intervention k or intervention k' as superior for this stratum.

The probabilities for each comparison will be reported alongside the medians and 95% highest density credible intervals of the (difference) distributions.

Scheduled analyses and DSMC

The first scheduled analysis will be performed after 260 participants have completed their ~28 day endpoint after

their final trial vaccine dose and the results from the batched blood samples are available from the laboratory analysis. Thereafter, scheduled analyses will be performed after every 100 additional participants with available ~28 day laboratory results for the remainder of the trial. Data will be extracted from the BOOST-IC database immediately prior to the commencement of each scheduled analysis and the BOOST-IC analytic team will prepare a report containing all pre-specified analyses for which the data is available (including immunogenicity and safety data) for the DSMC in a closed report. An open report containing safety data without reference to the intervention received will be provided to trial investigators. The DSMC will make recommendations to the BOOST-IC trial steering committee based on an assessment of both the open and closed reports.

Precision

We will compute the **precision** of each quantity of interest to be assessed against pre-specified precision criteria. The precision, ρ_{jklt}, of the posterior distribution of θ_{jklt} is defined as the width of 95% highest density credible interval:

$$\rho_{jklt} = \widehat{\theta_{jklt,U}} - \widehat{\theta_{jklt,L}} \tag{34}$$

Here, $\widehat{\theta_{jklt,U}}$ and $\widehat{\theta_{jklt,L}}$ represent the upper and lower bounds, respectively, of the 95% highest density credible interval of the posterior distribution of θ_{jklt}. High values of ρ_{jklt} indicate high uncertainty, and therefore low precision, in the estimation of θ_{jklt}. Similarly, low values of ρ_{jklt} indicate low uncertainty, and therefore high precision, in the estimation of θ_{jklt}.

We define the precision criteria for estimand 01 (log scale) for the immunocompromised subpopulation j as:

$$\rho_{jklt} < 0.3 \quad \forall k \in \boldsymbol{K}, l \in \boldsymbol{L}, t \in \boldsymbol{T} \tag{35}$$

Here, we say that the precision criteria has been met for an immunocompromised subpopulation j if the width of the 95% highest density credible interval for the mean parameter θ_{jklt} is less than 0.3 units on the $\log_{10}$ scale for all currently available interventions, trial vaccine dose numbers and baseline serostatus levels. Assuming the posterior distribution is approximately symmetric, on the untransformed scale (U/mL), this equates to lower and upper bounds corresponding to a multiplicative reduction of 0.668 or a multiplicative increase of 1.496 to the mean. This threshold was determined through discussions with clinicians and in conjunction with extensive computer simulations demonstrating its suitability across a range of plausible trial scenarios (supplementary material).

Trial adaptations

At each scheduled analysis, the precision will be assessed against the precision criteria for each immunocompromised subpopulation for estimand 01. If the precision criteria is met, i.e. the precision is sufficiently high, within an immunocompromised subpopulation then *recruitment will be ceased* into that immunocompromised subpopulation. The outcomes of the precision criteria assessments will be included in the report provided to the trial investigators and DSMC. If the precision criteria is not met, then recruitment will be ceased to an immunocompromised subpopulation once there are at least 320 total participants randomised from that subpopulation.

Trial commencement

At commencement, the BOOST-IC trial enrolled participants from the HIV, SOT and HM immunocompromised subpopulations and randomised each to receive one or two dose schedules of the Moderna Spikevax Original/Omicron BA.1 vaccine.

To validate the trial design prior to trial commencement, computer simulations were generated to determine the trial operating characteristics under a range of plausible scenarios (supplementary material). The objective of the simulation study was to assess the choice of precision threshold (i.e. whether or not adaptations were triggered due to sufficient precision within an immunocompromised subpopulation prior to maximum recruitment). Trial simulations were explored by varying the number and timing of sequential analyses, precision criteria threshold, recruitment rates and intervention detectable proportions, conditional means and standard deviations. The simulations for each scenario assumed full recruitment up to a maximum of 960 participants (320 per immunocompromised subpopulation) including 5% loss to follow up between randomisation and endpoint collection (for estimand 01). We chose conditional mean and standard deviation SARS-CoV-2 anti-spike IgG concentrations to be similar to those in the COV-BOOST trial publication [21]. The standard deviation for the simulated $\log_{10}$ SARS-CoV-2 anti-spike IgG concentration was varied from 0.3 to 0.5 and a weak correlation of $r_l = 0.3$ was assumed.

The simulation results including the median precision and mean sample sizes are presented in Table 4. As anticipated, an increase in the proportion of participants with a detectable response led to an increase in the precision. Additional gains in precision are anticipated by the inclusion of covariates in the two-part model, and the ability to recruit greater numbers in patient subpopulations with higher variability when

Table 4 Median precision and mean sample sizes within immunocompromised subpopulations across simulation scenarios

Scenario	Patient group	Probability detectable response at day 28		SARS-CoV-2 anti-spike IgG concentration (U/mL)		Median precision	Mean sample size
		Baseline undetectable	Baseline detectable	Baseline undetectable	Baseline detectable		
Low	HIV	0.1	0.5	100	2000	0.37	320
	SOT	0.1	0.5	100	300	0.37	320
	HM	0.1	0.5	100	300	0.37	320
Moderate	HIV	0.3	0.8	200	5000	0.29	320
	SOT	0.3	0.8	200	500	0.29	320
	HM	0.3	0.8	200	500	0.29	320
High	HIV	0.5	0.8	300	10,000	0.26	320
	SOT	0.5	0.8	300	1000	0.26	320
	HM	0.5	0.8	300	1000	0.26	320

recruitment has stopped prior to reaching the maximum in other patient subpopulations.

Current state

The BOOST-IC trial opened recruitment on December 17, 2022, and has recruited 384 participants with follow-up ongoing as of May 2025. The first scheduled blinded analysis was conducted on the first 260 participants on August 21, 2024. Due to the availability of COVID-19 vaccines over time, participants have been randomised to Moderna Spikevax Original/Omicron BA.1, Pfizer Comirnaty Original/Omicron BA.1, Moderna Spikevax Original/Omicron BA.4/5, Pfizer Comirnaty Original/Omicron BA.4/5, Moderna Spikevax Omicron XBB.1.5 and Pfizer Comirnaty Omicron XBB.1.5 (note that at no point was a Novavax intervention included). The current version of the protocol is version 8.1 (June 28, 2024).

Discussion

The BOOST-IC trial follows other contemporaneous platform trials, including the Australasian COVID-19 Trial (ASCOT) [25], the Randomized Embedded Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP CAP) [26], the Staphylococcus Network Adaptive Platform trial (SNAP) [19, 27] and the PICOBOO trial [7], to drive the way forward for innovative, resource-efficient trial designs in the clinical research space. In common with the PICOBOO trial, we aim to inform COVID-19 policy in Australia, and compliment the global evidence supporting vaccine schedules in immunocompromised individuals. This paper provides a detailed account of the statistical elements and design of the BOOST-IC trial. As the trial progresses, interim statistical implementation guides will be made available online. The purpose of the statistical implementation guides will be to detail to exact specifications of the trial structure, analysis populations and statistical modelling at the time of each scheduled analysis, in contrast to the more general overview of the statistical elements provided here. A full statistical analysis plan will be produced and made available prior to trial conclusion that details the final statistical analysis. We aim to provide transparency concerning all analyses and a detailed, generalisable Bayesian model for other researchers in the changing COVID-19 vaccine landscape.

Abbreviations

ASCOT	Australasian COVID-19 trial
BOOST-IC	Bringing Optimised COVID-19 Vaccine Schedules to Immunocompromised Populations
ChAdOx1 nCov-19	Oxford-AstraZeneca vaccine
CD	Cluster of differentiation
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus 2019
COV-BOOST	Comparing COVID-19 booster vaccinations
DSMC	Data safety and monitoring committee
HIV	Human immunodeficiency virus
HM	Haematological malignancies
HMC	Hamiltonian Monte Carlo
IgG	Immunoglobulin G
IS	Immunological subset
IS-S	Immunological subset subgroup
LKJ	Lewandowski-Kurowicka-Joe
MCMC	Markov-chain Monte Carlo
MI	Modified intention-to-treat
MI-S	Modified intention-to-treat subgroup
NUTS	No-U-Turn Sampler
PICOBOO	Platform trial in COVID-19 priming and boosting
REMAP-CAP	Randomized Embedded Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SNAP	Staphylococcus Network Adaptive Platform trial
SOT	Solid organ transplants
SP	Safety population
VoC	Variants of concern

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08965-w.

Supplementary Material 1.

Acknowledgements
The BOOST-IC team would like to thank the participants and families who contributed to this study and the Alfred Ethics Committee for facilitating reviews to allow the trial to progress in a timely manner. We extend our gratitude to the BOOST-IC investigators, study staff and the DSMC.

Authors' contributions
MD and JAM conceived of and drafted the manuscript with input from all co-authors, and developed the statistical models. JAM is the senior statistician on the trial. All authors are members of the BOOST-IC Trial Steering Committee or Analytic Team and contributed substantially to the BOOST-IC trial design detailed in this manuscript. All authors have read and approved the final version.

Funding
Funding for this trial was provided by the Medical Research Future Fund (MRF2014921). The funding bodies played no role in the design of the study, nor the collection, analysis, or interpretation of the data or manuscript preparation. TS is supported by an MRFF Investigator Award (MRF1195153). Preliminary statistical design work by MD, JM and TS was supported by a grant from the Snow Medical Foundation. MD is supported by a NHMRC Postgraduate Research Award (APP2022557), an AusTriM Postgraduate Top-up Scholarship, a Stan and Jean Perron Top-up Scholarship, a Statistical Society of Australia PhD Top-up Scholarship and a Wesfarmers Centre of Vaccines and Infectious Diseases Top-up Scholarship.

Data availability
Access to data will be granted to study investigators and authorised representatives from the sponsor and the regulatory authorities to allow trial-related monitoring, audits, and inspections to occur. BOOST-IC will also comply with relevant jurisdictional and academic requirements relating to access to data, as applied at the time that the data are generated.

Declarations

Ethics approval and consent to participate
Ethics approval for the conduct of this study has been provided by the Alfred Ethics Committee (122/22). Informed consent to participate will be obtained from all participants in either written or electronic form.

Consent for publication
No identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent form are available from the corresponding author on request and will be available on the trial website.

Competing interests
The authors declare that they have no competing interests.

Received: 28 May 2025 Accepted: 3 July 2025
Published online: 25 July 2025

References

1. Weerasuria M, Ko C, Ehm A, O'Bryan J, et al. The impact of the COVID-19 pandemic on people living with HIV in Victoria, Australia. AIDS Res Hum Retrovir. 2021;37(4):322–8.
2. Mohamed K, Rzymski P, Islam MS, Makuku R, Mushtaq A, Khan A, et al. COVID-19 vaccinations: The unknowns, challenges, and hopes. J Med Virol. 2022;94(4):1336–49.
3. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25):2881–92.
4. Bhaskaran K, Rentsch CT, MacKenna B, Schultze A, Mehrkar A, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. Lancet HIV. 2021;8(1):24–32.
5. Yamanaga S, Shimata K, Ohfuji S, Yoshikawa M, Natori Y, Hibi T, et al. Excess mortality in COVID-19-affected solid organ transplant recipients across the pandemic. Am J Transplant. 2024. https://doi.org/10.1016/j.ajt.2024.03.016.
6. Slaoui M, Hepburn M. Developing Safe and Effective Covid Vaccines – Operation Warp Speed's Strategy and Approach. N Eng J Med. 2020;383(18):1701–3.
7. McLeod C, Ramsay J, Flanagan KL, Plebanski M, Marshall H, Dymock M, et al. Core protocol for the adaptive Platform Trial In COVID-19 Vaccine priming and BOOsting (PICOBOO). Trials. 2023;24(202). https://doi.org/10.1186/s13063-023-07225-z.
8. Berry SM, Connor JT, Lewis RJ. The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments. JAMA. 2015;313(16):1619–20. https://doi.org/10.1001/jama.2015.2316.
9. Saville BR, Berry SM. Efficiencies of platform clinical trials: A vision of the future. Clin Trials. 2016;13(3):358–66. https://doi.org/10.1177/1740774515626362.
10. Meyer EL, Mesenbrink P, Dunger-Baldauf C, Li Y, Posch M, König F. The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review. Clin Ther. 2020;42(7):1330–60. https://doi.org/10.1016/j.clinthera.2020.05.010.
11. Griffin DWJ, Dymock M, Wong G, Morrissey CO, Lewin SR, et al. Bringing optimised COVID-19 vaccine schedules to immunocompromised populations (BOOST-IC): study protocol for an adaptive randomised controlled clinical trial. Trials. 2024;25(485). https://doi.org/10.1186/s13063-024-08315-2.
12. Dymock M, McLeod C, Richmond P, Snelling T, Marsh JA. Statistical considerations for the platform trial in COVID-19 vaccine priming and boosting. Trials. 2024;25(507). https://doi.org/10.1186/s13063-024-08343-y.
13. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian Data Analysis (3rd Edition). United States: Chapman and Hall/CRC; 2013. https://doi.org/10.1201/b16018.
14. McGlothlin AE, Viele K. Bayesian Hierarchical Models. JAMA. 2018;320(22):2365–6. https://doi.org/10.1001/jama.2018.17977.
15. Berry SM, Carlin BP, Lee JJ, Muller P. Bayesian Adaptive Methods for Clinical Trials (1st Edition). United States: CRC Press; 2010. https://doi.org/10.1201/EBK1439825488.
16. E9(R1) Statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials. https://www.fda.gov/media/108698/download. Accessed 20 Feb 2023.
17. Saville BR, Berry DA, Berry NS, Viele K, Berry SM. The Bayesian Time Machine: Accounting for temporal drift in multi-arm platform trials. Clin Trials. 2022;19(5):490–501. https://doi.org/10.1177/17407745221112013.
18. Bofill Roig M, Krotka P, Burman CF, Glimm E, Gold SM, et al. On model-based time trend adjustments in platform trials with non-concurrent controls. BMC Med Res Methodol. 2022;22(228). https://doi.org/10.1186/s12874-022-01683-w.
19. Mahar RK, McGlothlin A, Dymock M, Lee TC, Lewis RJ, et al. A blueprint for a multi-disease, multi-domain Bayesian adaptive platform trial incorporating adult and paediatric subgroups: the Staphylococcus aureus Network Adaptive Platform trial. Trials. 2023;24(795). https://doi.org/10.1186/s13063-023-07718-x.
20. Lewis RJ, Wears RL. An introduction to the Bayesian analysis of clinical trials. Ann Emerg Med. 1993;22(8):1328–36.
21. 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;298(10318):2258–76. https://doi.org/10.1016/S0140-6736(21)02717-3.
22. Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, et al. Stan: A probabilistic programming language. J Stat Softw. 2017;76(1):1-32.

23. Gabry J, Češnovar R, Johnson A. cmdstanr: R Interface to 'CmdStan'; 2022. https://mc-stan.org/cmdstanr/, https://discourse.mc-stan.org. Accessed 31 Jan 2025.
24. Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2022. https://www.R-project.org/. Accessed 31 Jan 2025.
25. Denholm JT, Venkatesh B, Davis J, Bowen AC, Hammond NE, Jha V, et al. ASCOT ADAPT study of COVID-19 therapeutics in hospitalised patients: an international multicentre adaptive platform trial. Trials. 2022;75(1014). https://doi.org/10.1186/s13063-022-06929-y.
26. Angus DC, Berry S, Lewis R, Al-Beidh F, Arabi Y, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study Rationale and Design. Ann Am Thorac Soc. 2020;17(7). https://doi.org/10.1513/AnnalsATS.202003-192SD.
27. Tong SYC, Mora J, Bowen AC, Cheng MP, Daneman N, Goodman AL, et al. The Staphylococcus aureus Network Adaptive Platform Trial Protocol: New Tools for an Old Foe. Clin Infect Dis. 2022;75(11):2027–34. https://doi.org/10.1093/cid/ciac476.

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