SNAP Adjunctive Domain Statistical Analysis Plan Version 1.0

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Contents

VERSION HISTORY

VERSION 1.0 : 19th December 2025

Initial release.

Abbreviations

Abbreviation	Explanation
AT	Analytic Team
DSMC	Data Safety and Monitoring Committee
GTSC	Global Trial Steering Committee
RIG	Reporting Implementation Guide
SAP	Statistical Analysis Plan
SIG	Statistical Implementation Guide
SMP	Statistical Methods Paper

1 Introduction

This statistical analysis plan (hereafter known as the *SAP*) sets out how the data for the SNAP Adjunctive Treatment domain will be analysed and reported. This may occur when recruitment to any domain interventions is ceased for any subgroup due to exceeding decision thresholds for superiority or futility, reaching maximum domain recruitment or following recommendation(s) from the Data Safety and Monitoring Committee (hereafter known as *DSMC*). Due to the nature of the trial design, separate trial reports may be generated from this SAP at different time points, however, this is outside the scope of this SAP and details of the requirements for each report are documented in the Reporting Implementation Guide (herafter referred to as the *RIG*). Reports will include:

- the reason for the report and an outline of what has previously been reported for the SNAP platform;
- participant eligibility and the date of the datacut, including the date that the last report-eligible participant was recruited;
- CONSORT flowchart indicating all SNAP participants that may contribute to the primary analysis;
- the combinations of silos (PSSA, MSSA, MRSA), subgroups (adult, paediatric) and interventions for which results will be included in the report, i.e. which results are being unblinded and which will remain blinded to maintain trial integrity in the other silos/subgroups/intervention combinations.

The SAP builds on the information in existing trial documentation and provides greater detail for defining the estimands, the parameterisation in the statistical models, sub-group analyses and additional pre-specified estimands not included in the protocol or protocol appendices.
None of the SNAP SAPs are standalone documents; they are intended to be read in conjunction with, and informed by, the core protocol, the domain specific appendices, subgroup-specific appendices, the statistical appendix to the core protocol, the statistical implementation guide(s) (hereafter known as the *SIGs*), and the SNAP Standardised Derived Variables document, all of which are publicly available at the trial website (https://www.snaptrial.com.au/).
The *SAP* was written by statisticians and investigators without access to the SNAP data or domain-specific results from scheduled analyses. It was reviewed by members of the statistical subcommittee, members of the Global Trial Steering Committee (hereafter known as *GTSC*) and SNAP investigators who are similarly blinded to individual intervention assignments in the SNAP platform and results from scheduled analyses that are reported to the DSMC.

2 Purpose and scope of plan

The primary estimand, the core secondary estimands, the domain-specific secondary estimands, paediatric-specific estimands, pregnancy-specific appendix, microbiological appendix and people who inject drugs appendix all fall within the scope of this plan. These planned analyses may be included in a single report or across multiple reports, which will be detailed in the RIG, and may included in any arising manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support the planned analyses. However, any post-hoc or unplanned analyses not specified herein will be identified as such in any statistical reports and manuscripts for publication. The SAP is structured to minimise replication across trial documents and, therefore, is not a standalone document. It needs to be read in conjunction with the appropriate versions of the core protocol and associated appendices, statistical implementation plan, published statistical models and standardised derivation of variables as detailed below. When referring to specific model parameters, this SAP utilises the

statistical modelling definitions provided in Mahar et al (2023, see below). Throughout the SAP, the reader is directed to the appropriate sections of these documents for essential definitions, statistical modelling and derivation of variables for analysis and reporting.
This SAP was prepared in conjunction with:

- Core protocol for SNAP Version 2.0
- Domain-Specific Appendix: Adjunctive Treatment for SNAP Version 2.0
- Microbiology Appendix Version 2.0
- Paediatric-Specific Appendix Version 3.0
- People Who Inject Drugs (PWID) Appendix Version 3.0
- Pregnancy-Specific Appendix Version 3.0
- Statistical Analysis Appendix for SNAP Version 2.0
- SNAP Statistical Implementation Guide (all versions). Hereafter known as SIG.
- SNAP Derived Variables Version 2.0 (final draft available at time of this SAP publication).
- A blueprint for a multi-disease, multi-domain Bayesian adaptive platform trial incorporating adult and paediatric subgroups: the Staphylococcus aureus Network Adaptive Platform trial (https://doi.org/10.1186/s13063-023-07718-x). Hereafter known as the statistical methods paper (SMP).

The SAP does not address domain-specific estimands from the Backbone (all silos), Early Oral Switch (EOS), and PET/CT domains, which will be covered in separate SAP's. This SAP does not include analysis of registry data but is restricted to individuals who have at least one randomisation revealed for any domain. The Health Economics Appendix and all substudies will be addressed in separate documents.

Statistical modeling will be based on the details provided in the SMP, however, the Analytic Team may collapse categories or remove model parameters where there are low or zero frequencies to account for sparse data. Where there is any conflict between the information contained in this SAP and the documents listed above, the information in this SAP takes precedence.

3 Trial population

Trial populations for the adjunctive domain are described, incorporating pooling (complete information sharing) over the silos. The data for all platform analytic eligible participants are included in the analysis of each estimand, unless stated otherwise in the estimand sections below. Overall eligibility for the adjunctive domain, for any silo, is included as a parameter in the primary statistical model.
Platform analytic eligibility is defined as participants who meet the inclusion and exclusion criteria detailed in the core protocol **and** who are classified as being members of one of the PSSA, MSSA or MRSA silos, based on the *Microbiology at platform entry* section below, **and** who have their randomisation revealed for at least one domain. For each report, as the trial recruitment is ongoing, report-eligible participants will be defined by a pre-specified date by which recruitment must have occurred in the *RIG*.
Adjunctive domain eligibility is defined as participants who are platform analytic eligible and meet the inclusion and exclusion criteria (including consent) for the adjunctive domain.
A CONSORT flowchart will be constructed, according to CONSORT guidelines. To maintain platform integrity for domains and/or silos not yet reported, the flowchart will only include intervention-level totals for the data in the current report and previously reported results.

4 Demographics and characteristics at platform entry

All demography and platform entry participant characteristics will be reported separately for adult and paediatric subgroups and summarised by domain-specific interventions.
For table 1, platform entry variables will include:

- age in years (footnote: at the time of platform screening)
- age categories as utilised in the model (footnote: at the time of platform screening)
- sex at birth (male/female)
- weight (kg) (footnote: measured or estimated)
- pregnant (yes/no) (footnote: Only consenting females where $12 <$ age (yrs) < 60 asked. Proportions in terms of total females at birth ($12 <$ age (yrs) < 60).)
- country of enrolment (refer to SIG for categories)
- diabetes mellitus (yes/no)
- chronic kidney disease (yes/no) (footnote: defined as eGFR < 50 mL/min/1.73m^2)
- end stage kidney disease (yes/no) (footnote: defined as receiving haemodialysis at least once a week or continuous peritoneal dialysis)
- liver cirrhosis (yes/no)
- cancer requiring any surgical or medical therapy within the past 12 months (yes/no) (footnote: excluding non-melanoma skin cancers)
- dementia (yes/no) (footnote: any severity)
- iatrogenic immunosuppression (yes/no) (footnote: Within past 3 months has received any of the following: Prednisolone $>$ 0.5mg/kg/day (or the equivalent) for more than 14 days / Cyclosporin, tacrolimus or sirolimus / Azathioprine or mycophenolate / Cyclophosphamide / Leflunomide or methotrexate / Monoclonal antibodies (e.g. infliximab, etanercept, adalimumab, rituximab) / Cancer chemotherapy / Bone marrow transplantation / Other immunosuppressive agents equivalent to above / AIDS)
- limitations to care (yes/no) (footnote: Active orders or advanced care directive limiting resuscitation with intensive care unit level interventions, e.g. DNR, NFR, DNAR)
- an implanted prosthesis or endovascular device (yes/no) (footnote: with specific devices, i.e. Mechanical heart valve/Bioprosthetic heart valve/Permanent pacemaker or other implantable cardiac device/Other intravascular foreign material (footnote: Not including IV or central lines, whether simple or tunneled)
- previous infective endocarditis (yes/no)
- underlying cardiac abnormality predisposing to endocarditis (yes/no) (footnote: Not related to prosthesis or implanted device (For example, aortic or mitral valve disease, coarctation of the aorta, rheumatic heart disease, or ventricular septal defect))
- injecting drug use in the last 6 months (adults only) (yes/no) (footnote: excluded Singapore)
- receipt of antibiotics between index blood culture and platform entry, (yes/no)

- Pitt bacteremia score (footnote: derived from variables relating to the 48 hours prior to platform entry, i.e. need for mechanical ventilation, cardiac arrest, use of vasdooropressors, mental state, most abnormal temperature, lowest systolic blood pressure.) Details available in SNAP Derived Variables (Version 2.0).
- in intensive care unit (yes/no) (footnote: Includes all inpatient areas where there is capacity for organ support including invasive or non-invasive ventilation, vasopressors/inotropes and higher nursing ratios than the normal ward.)
- time from index blood culture collection to platform entry (hours)
- time from index blood culture collection to adjunctive domain entry (hours)
- time to positivity of index blood culture (hours)
- C-reactive protein (mg/L)

The above demography and platform entry participant characteristics will also be reported separately for adult and paediatric subgroups and summarised by domain-specific interventions with and without complete outcome data for core estimand 1.

5 Antibiotic use prior to platform entry

Antibiotics administered in the time period between index blood collection and platform entry will be summarised by antibiotic name and backbone-domain intervention (revealed allocations for the non-adjunctive domains will only be included if those domains and/or silos have previously been reported), and reported separately for each adjunctive domain intervention.

6 Microbiology at platform entry

Methicillin-susceptibility and penicillin-susceptibility was determined in accordance with the microbiology appendix or additionally specified in the region-specific appendix, which may include disc diffusion, mecA PCR, nitrocefin test, and/or automated methods. For further details see the Microbiology Appendix.

Silo classification is based on index blood culture for participants who have their randomisation revealed to the backbone domain. Silo classification is based on information available up to platform Day 7 for participants without randomisation revealed to the backbone domain. For further information see silo section of the SNAP Derived Variables (Version 2.0).

A participant may have been misclassified due to:

- Unrecognized mixed culture
- Technical laboratory reporting or handling issues
- Initial misinterpretation of disc diffusion zone or edge

Silo misclassifications are recorded between platform days 1-7 in the CRF and may also be captured in either patient summary notes in the CRF or from site email correspondence from information which becomes available after the initial classification (available in the Silo Discrepancies document). They are explicitly defined by adherence to protocol or non-adherence to protocol in the *Misclassification of silo* section below. Any information on the determination of silo that was later contradicted by central laboratory review is excluded and no adjustments will be made in the estimands.

7 Randomisations revealed in the other platform domains

For each intervention in the adjunctive domain, the number of revealed randomisations for each intervention in the other platform domains will be produced for each silo separately. **To maintain trial integrity, the distribution of revealed allocations for the non-adjunctive domains will only be included if those domains and/or silos have previously been reported.** The table will be generated for adjunctive domain eligible participants with separate columns for interventions and rows for:

- Backbone domain
- Early oral switch domain
- PET/CT domain
- Future platform domains

8 Estimands

8.1 General principles and definitions

Time of platform entry is defined as the date of generation of the concealed randomisations for each participant, which occurs closest to the time of consent and is recorded as a date-time variable. This differs from the date of domain-specific randomisation reveals (see SNAP Derived Variables (Version 2.0)). The timing of endpoints are defined relative to platform entry in order to standardise timing across all domains, unless stated otherwise in the protocol appendices or domain-specific estimand(s). In rare instances, an endpoint may be met prior to the date of domain-specific randomisation reveal.

Loss to follow-up is defined as a participant who has unknown vital status at platform day 90 and/or missing data after hospital discharge at the time of data cut. For time to event outcomes, the date that a participant with unknown event status at the time of endpoint becomes lost to followup is at the derived last known date alive (see SNAP Derived Variables (Version 2.0) for futher details). The trial is ongoing and missing values may be updated later in the trial (e.g. if supplemented with data linkage to registry data) and be included in subsequent reports.

8.2 Non-adherence to protocol

8.2.1 Randomisation (for the core platform or adjunctive domain) of ineligible participant

Where a protocol deviation identifies a participant who was randomised and/or had an intervention assignment revealed, but evidence after randomisation indicated that this participant was ineligible for the core platform or backbone domain, these participants are considered to be non-adherent to protocol.

8.2.2 Misclassification of silo

Details about the definition of silo misclassifications are provided in the *Microbiology at platform entry* section of this document. The following misclassifications are identified as either adherence or non-adherence to protocol:

- MSSA initially recorded, actual silo is MRSA: protocol non-adherence

- MSSA initially recorded, actual silo is PSSA: protocol adherence
- PSSA initially recorded, actual silo is MRSA: protocol non-adherence
- PSSA initially recorded, actual silo is MSSA: protocol non-adherence
- MRSA initially recorded, actual silo is MSSA: protocol non-adherence
- MRSA initially recorded, actual silo is PSSA: protocol non-adherence

8.2.3 Non-adherence to adjunctive domain interventions

Adherence to adjunctive domain interventions is assessed for those patients who were observed to platform day 7. As such, individuals who died (including those not known to be alive on day 7), withdrew, or were discharged to alternative acute care where data are not available before day 7 are considered not to be adherent and are not considered part of the analysis population for Domain-specific Estimand B.1. All participants who were on trial at day 7 and do not meet the assigned-intervention adherence criteria below will be defined as non-adherent. Similar assigned-intervention adherence criteria will be defined for any new adjunctive domain interventions that may be included at a future date. For currently active treatments refer to the *SIG*.

- **Assigned to control (no adjunctive treatment):**
  In the non-clindamycin group, protocol adherence is defined as < 2 doses of clindamycin/lincomycin/linezolid between confirmation of domain eligibility and the end of platform day 7. Note that this is a change from the domain specific appendix which specified end of platform day 14.
- **Assigned to clindamycin:**
  In the clindamycin group, protocol adherence is defined as those participants who have received at least 10 doses of clindamycin/lincomycin between confirmation of domain eligibility and the end of platform day 5.

8.2.4 Limitations of non-adherence definitions

The lack of dummy or placebo in the control arm and the pragmatic nature of this trial make it challenging to utilise a definition of adherence that is applicable to all participants in the domain. Given the desire to assess the treatment effect among those with adherence across the first seven days, we do not consider individuals who were bit observed to platform day 7 to contribute to the target population, which leads to the exclusion of deaths that occur in the first seven days. Domain-specific Estimand B.1 makes the assumption that treatment allocation does not affect protocol adherence. We acknowledge there are other methods to look into this with alternative assumptions (see https://pubmed.ncbi.nlm.nih.gov/35851717/) but these are outside the scope of this SAP. Any alternate definitions of adherence will be clearly identified as post hoc.

8.3 Intercurrent events common to estimands

Intercurrent events (*IE*) occur between randomisation and outcome assessment and may either preclude or effect the endpoint. Some anticipated intercurrent events may be common to many estimands and are listed here (IE.1 to IE.6) to avoid replication below. However, the strategies to account for these intercurrent events may differ between the estimands. Although other potential intercurrent events were perceived, only those that could be identified from the current platform data collection are included given the pragmatic nature of the trial.

- **IE.1:** non adherence to assigned intervention between platform entry and Platform day 7 due to site procedures or environment.

- **IE.2:** non adherence to assigned intervention between platform entry and Platform day 7 due to inadequate clinical response.
- **IE.3:** non adherence to assigned intervention between platform entry and Platform day 7 due to clinician-indicated adverse event or serious adverse reaction (SAR) report.
- **IE.4:** loss to follow up or withdrawal.
- **IE.5:** all-cause death.
- **IE.6:** discharge to subsequent acute care site where further clinical data is unavailable.

Reasons for change to adjunct-domain revealed allocation are only collected if the change is not clinically indicated and a protocol deviation form is filled out. IE.1, IE.2 and IE.3 all receive the same handling strategy throughout, so misclassification within these three IEs will not impact the analysis. No reasons are available for trial withdrawal or loss to follow-up, and data collection at platform day 90 is used as a surrogate for information gathered on an end of study form. The intention is for consistency with the SNAP Backbone Domain for PSSA and MSSA silos Statistical Analysis Plan regarding the IE handling strategy for the core estimands, any deviations are indicated in this document.

8.4 Core Estimand 1

Objective: To evaluate the effect of revealed randomised interventions for the adjunctive domain compared to control, on the probability of all-cause mortality at 90 days after platform entry.

Target population: Adjunctive domain eligible participants, excluding participants with missing mortality status at Day 90.

Endpoint: All-cause mortality at 90 days after platform entry.

Analysis: Binary endpoint modeled using a Bernoulli distribution with a logistic link function (full details provided in the *SMP* and the *SIG*).

Population level summaries: Conditional log odds ratio of the endpoint for intervention compared to domain-control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data at Day 90 may be due to IE.4 or IE.6 and these participants are excluded from the analysis (see target population above).

Sensitivity estimands: The analysis may be repeated with up to two different assumptions pertaining to individuals with unknown mortality status at day 90:

- Sensitivity estimand 1.1: Anyone without evidence of survival will be assumed to have died, a composite strategy for IE.4 and IE.6.

- Sensitivity estimand 1.2: Anyone without evidence of death will be assumed to have survived, a composite strategy for IE.4 and IE.6.

The analysis that favours the control arm (no adjunctive treatment) will be considered the key sensitivity estimand.

Sensitivity estimand 1.3: Replacing the prior distributions with those specified below. This aligns with the *Bayesian Analysis Reporting Guidelines* (Kruschke 2021, https://pmc.ncbi.nlm.nih.gov/articles/PMC8526359/ *Reporting sensitivity analysis* (Step 5), and includes weakly uninformative priors for the regression parameters, which provide enough structure to stabilize inference without overpowering the data (Gelman et al. 2013, Bayesian Data Analysis, 3rd ed). In addition, all information sharing (aka Bayesian borrowing) will be removed in this sensitivity analysis. The priors are specified below, continuing with the mathematical notation defined in the manuscript by Mahar et al (2023).

8.4.1 Priors for reference log-odds

The log-odds for domain-specific reference interventions d_{kj} for each silo s and subgroup u already have weakly informative priors specified, therefore, these remain unchanged as follows:

$$\alpha_{s,u} \sim N(-2, 10^2)$$

8.4.2 Priors for interventions

The priors for the log-odds ratios (β) for domain-specific interventions d_{kj} for each silo s and subgroup u are changed to prevent information sharing between adult and paediatric subgroups. In addition, similar to the backbone domain, there is no information sharing between the silos for the early oral switch domain. For the adjunctive domain, data is still pooled over the silos, but separately for adults and paediatrics. For each prior, the location parameter remains centered on zero, but the variance is increased to 10^2.

For backbone and early oral switch domains:

$$\beta_{s,u,d_{kj}} \sim N(0, 10^2)$$

For adjunctive domain:

$$\beta_{u,d_{kj}} \sim N(0, 10^2)$$

8.4.3 Priors for domain eligibility

The priors for the log-odds ratios for domain eligibility γ_{s,u,D_k} for each silo s and subgroup u are independent normal distributions. For each prior, the location parameter remains centered on zero, but the variance is increased to 10^2.

$$\gamma_{s,u,D_k} \sim N(0, 10^2)$$

8.4.4 Priors for inter-domain intervention interactions

The priors for the log-odds ratios for two-way interactions between inter-domain interventions $\psi_{s,u,d_{kj},d_{k'j}}$ for each silo s and subgroup u are independent normal distributions. For each prior, the location parameter remains centered on zero, but the variance is increased to 10^2.

$$\psi_{s,u,d_{kj},d_{k'j}} \sim N(0, 10^2)$$

8.4.5 Priors for regions and countries

Whilst the statistical model allows for the flexibility to model countries nested within region, the current recruitment of sites (i.e. few countries within each region) supports modelling of each country separately. Therefore, the parameters for the log-odds ratios for regions δ_r are removed (constrained to zero). The priors for the log-odds ratios for countries ω_c are independent normal distributions with location parameters centered on zero, and variances of 10^2.

$$\omega_c \sim N(0, 10^2)$$

8.4.6 Priors for covariates

The priors for the log-odds ratios for the covariates (e.g., age) $\theta_{Z_k, z_{kj}}$ are independent normal distributions. The priors remain unchanged location parameter centered on zero and a variance of 10^2.

$$\theta_{Z_k, z_{kj}} \sim N(0, 10^2)$$

8.4.7 Priors for epochs

The priors for the log-odds ratios for the time epochs terms in the statistical model remain unchanged.

$$\phi_{N_T} = 0$$

$$\phi_{t-1} \sim N(\phi_t, \tau_t^2)$$

$$\tau_t^2 \sim Inv.Gamma(0.25, 0.1)$$

Note that these sensivity estimands were not present in the Statistical Analysis Plan for the SNAP Backbone Domain for PSSA and MSSA silos.

8.5 Core Estimand 2

This estimand has been superseded by domain-specific Estimand B.1. Core estimands with target populations defined by adherence to protocol and treatment regimes across **all** domains are not appropriate and difficult to interpret.

8.6 Core Estimand 3

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 14 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants with missing mortality status at Day 14.

Endpoint: All-cause mortality at 14 days after platform entry.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: As for Core Estimand 1.
As for Core Estimand 1, except missing endpoint data at Day 14 may be due to IE.4 or IE.6 and these participants are excluded from the analysis (see target population above).

Sensitivity analyses: None planned.

8.7 Core Estimand 4

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 28 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants with missing mortality status at Day 28.

Endpoint: All-cause mortality at 28 days after platform entry.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: As for Core Estimand 1.
As for Core Estimand 1, except missing endpoint data at Day 28 may be due to IE.4 or IE.6 and these participants are excluded from the analysis (see target population above).

Sensitivity analyses: None planned.

8.8 Core Estimand 5

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 42 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants with missing mortality status at Day 42.

Endpoint: All-cause mortality at 42 days after platform entry.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: As for Core Estimand 1.
As for Core Estimand 1, except missing endpoint data at Day 42 may be due to IE.4 or IE.6 and these participants are excluded from the analysis (see target population above).

Sensitivity analyses: None planned.

8.9 Core Estimand 6

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of survival (time to all-cause mortality), censored at 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants.

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Endpoint: Time to all-cause mortality, censoring participants who died at their date of death if known or at the date of derived last known alive + 1 day if unknown date of death, and otherwise censoring participants at date of withdrawal/loss-to-follow-up or Day 90, whichever occurs first.

Analysis: Time to event endpoint modeled using a Weibull proportional hazards (accelerated failure) model with a log link function (full details provided in the *SMP* and the *SIG*.

Population level summaries: Conditional log hazards ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data at Day 90 may be due to IE.4 or IE.6 and these participants are right censored at the date of withdrawal or date of discharge to subsequent acute care site or date of acute index hospital discharge, as appropriate.

Sensitivity analyses: None planned, unless the assumption of proportional hazards is considered inappropriate by the analytic team.

8.10 Core Estimand 7

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of total index hospitalisation (time to **discharge alive** for total index hospitalisation), censored at 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants.

Endpoint: Time to discharge alive for total index hospitalisation, censoring at the time of discharge (including HITH/COPAT/OPAT), withdrawal/loss-to-follow-up or Day 90, whichever occurs first.

Analysis: As for Core Estimand 6.

Population level summaries: As for Core Estimand 6.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence

or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6; these participants are right censored at the date of withdrawal or date of discharge to subsequent acute care site (HITH/COPAT/OPAT), as appropriate. This excludes hospital re-admissions following the total index hospitalisation, even if within 90 days of platform entry. All deaths (IE.5) during the total index hospitalisation will be considered a 90-day follow-up period without discharge alive.

Sensitivity analyses: None planned, unless the assumption of proportional hazards is considered inappropriate by the analytic team.

8.11 Core Estimand 8

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of acute index hospitalisation (time to **discharge** for acute index hospitalisation), censored at 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants who survive until acute index hospital discharge.

Endpoint: Time to discharge for acute index hospitalisation, censoring at the time of discharge (excluding HITH/COPAT/OPAT), withdrawal/loss-to-follow-up or Day 90, whichever occurs first.

Analysis: As for Core Estimand 6.

Population level summaries: As for Core Estimand 6.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6; these participants are right censored at the date of withdrawal or date of discharge to subsequent acute care site (excluding HITH/COPAT/OPAT), as appropriate. This excludes hospital re-admissions following the total index hospitalisation, even if within 90 days of platform entry. Deaths (IE.5) during the acute index hospitalisation will be excluded (see target population).

Sensitivity analyses: None planned, unless the assumption of proportional hazards is considered inappropriate by the analytic team.

8.12 Core Estimand 9

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of total index hospitalisation (time to **discharge** for total index hospitalisation), censored at 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants who survive until total index hospital discharge.

Endpoint: Time to discharge for total index hospitalisation, censoring at the time of discharge (including HITH/COPAT/OPAT), withdrawal/loss-to-follow-up or Day 90, whichever occurs first.

Analysis: As for Core Estimand 6.

Population level summaries: As for Core Estimand 6.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6 and these participants are right censored at the date of withdrawal/derived last known date alive or date of last known to be in index hospital, respectively. This excludes hospital re-admissions following the total index hospitalisation, even if within 90 days of platform entry. Deaths (IE.5) during the total index hospitalisation will be excluded (see target population).

Sensitivity analyses: None planned, unless the assumption of proportional hazards is considered inappropriate by the analytic team.

8.13 Core Estimand 10

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of microbiological treatment failure between 15 and 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who do not survive to platform day 15 or who are without a microbiological treatment failure status between 15 and 90 days after platform entry.

Endpoint: Microbiological treatment failure, defined as positive sterile site culture for S. aureus [same silo as the index isolate] between 15 and 90 days after platform entry. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: A sterile site means any sites deep to the skin and skin structures that have been obtained in a sterile manner. No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6 or sample collection issues, or site/laboratory reasons for non-availability of microbiological testing results; these participants are excluded from the analysis (see target population above). A while-on-treatment strategy is used for death (IE.5) between 15 and 90 days after platform entry.

Sensitivity analyses: None planned.

8.14 Core Estimand 11

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of diagnosis of new foci between 15 and 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who do not survive to, or have withdrawn or are lost to followup by, platform day 15 or who have missing information on presence or absence of new foci between 15 and 90 days after platform entry.

Endpoint: Diagnosis of new foci between 15 and 90 days after platform entry. The presence of new foci is determined by the site investigator and can incorporate clinical, radiological, microbiological and pathological findings. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6 or diagnostic testing or sample collection issues, or site/laboratory reasons for non-availability of diagnostic or pathological or microbiological testing results; these participants are excluded from the analysis (see target population above). A while-on-treatment strategy is used for death (IE.5) between 15 to 90 days after platform entry.

Sensitivity analyses: None planned.

8.15 Core Estimand 12

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of diagnosis of C. difficile diarrhoea up to (and including) 90 days after platform entry, in participants ≥ 2 years of age.

Target population: Adjunctive Treatment domain eligible participants, excluding participants aged < 2 years of age or who have missing information on microbiological testing for C. difficile in the 90 days after platform entry.

Endpoint: Diagnosis of C. difficile diarrhoea as determined by a clinical laboratory in the 90 days following platform entry. Defined as a stool submitted to a clinical laboratory that tested positive for C. difficile toxin or toxin gene. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy,

adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Missing endpoint data may be due to IE.4 or IE.6 or sample collection issues, or site/laboratory reasons for non-availability of microbiological testing results; these participants are excluded from the analysis (see target population above). A while-on-treatment strategy is used for death (IE.5) in the 90 days after platform entry.

Sensitivity analyses: None planned.

8.16 Core Estimand 13

This estimand has been moved and labelled as domain-specific Estimand B.7. The endpoint of *Participants experiencing at least one Serious adverse reactions (SAR) defined as any SAE that is suspected to be related (as rated by the treating clinician) to a medicinal product used for S. aureus bacteraemia in the 90 days following platform entry* needs to be attributable to a single intervention within a domain rather than multiple interventions across domains.

8.17 Core Estimand 14

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of return to usual level of function on the modified functional bloodstream infection score (FBIS) between baseline (platform entry) and 90 days after platform entry in adults.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who are aged < 18 years or have missing baseline (platform entry) or Day 90 FBIS score due to withdrawal, loss to follow-up or site or participant availability.

Endpoint: Return to usual level of function 90 days after platform entry, defined as when the modified functional bloodstream infection score (FBIS) remained the same or improved from the best function in the 4 weeks prior to platform entry. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: As for Core Estimand 1.

Population level summaries: Conditional log odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Participants that did not survive to 90 days after platform entry (IE.5) are classified as did not return to usual level of function, irrespective of any FBIS scores recorded prior to death, i.e. a composite strategy. Missing endpoint data may be due to IE.4 or IE.6 or missing FBIS score at either platform entry or 90 days after platform entry; these participants are excluded from the analysis (see target population above).

Sensitivity analyses: None planned.

8.18 Core Estimand 15

This estimand has been moved and labelled as domain-specific Estimand B.8. The endpoint of *Desirability Of Outcome Ranking category (DOOR1, modified Antibiotic Resistance Leadership Group version), excluding the quality of life score, at platform Day 90* contains components that need to be attributable to a single intervention within a domain rather than multiple interventions across domains.

8.19 Core Estimand 16

This estimand has been moved and labelled as domain-specific Estimand B.9. The endpoint of *Desirability Of Outcome Ranking category (DOOR2, SNAP version), excluding the quality of life score, at platform Day 90* contains components that need to be attributable to a single intervention within a domain rather than multiple interventions across domains.

8.20 Core Estimand 17

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the clinician estimated number of antibiotic days (IV and/or oral/enteral) in the 90 days following platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who have a missing estimated number of antibiotic days due to withdrawal, loss to follow-up or participant transfer to a non-study care facility.

Endpoint: Clinician estimated number of antibiotic days, defined as the sum of the number of days on either IV and/or oral/enteral antibiotics from platform entry to 90 days after platform entry. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: No analyses will be performed.

Population level summaries: Median and inter-quartile range will be used to summarise the endpoint for each intervention for:

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or summaries as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Antibiotic prescriptions at hospital discharge will be assumed to be taken in full. Participants that did not survive to 90 days after platform entry (IE.5) will be recorded as the number of days alive and receiving antibiotic treatment; a while-on-treatment strategy. Similarly, participants who withdraw (IE.4) or are lost to follow-up (IE.6) prior to 90 days after platform entry will be recorded as the number of days in the study and receiving antibiotic treatment (including antibiotic prescriptions at discharge as appropriate).

Sensitivity analyses: None planned.

8.21 Core Estimand 18

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the cumulative proportion of days alive and free of antibiotics (IV and/or oral/enteral) in the 90 days following platform entry.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who have a missing proportion of days alive and free of antibiotics due to withdrawal, loss to follow-up or participant transfer to a non-study care facility.

Endpoint: Cumulative proportion of days alive and free of antibiotics (IV and/or oral/enteral) recorded at Day 90 day, excluding LTFU and withdrawals. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: No analyses will be performed.

Population level summaries: As for Core Estimand 17.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Antibiotic prescriptions at hospital discharge will be assumed to be taken in full (i.e. days not free of antibiotics). Participants that did not survive to 90 days after platform entry (IE.5) will be recorded as the proportion of days alive and not receiving antibiotic treatment; a while on treatment strategy. Participants who withdraw (IE.4) or are lost to follow-up (IE.6) are excluded from the summaries due to the potential for incomplete data on antibiotics prescriptions.

Sensitivity analyses: None planned.

8.22 Domain-specific Estimand B.1

Objective: To evaluate, within the domain, the effect of the intervention compared to the domain control, on the probability of all-cause mortality at platform day 90 in platform eligible participants who could have their adherence assessed at day 7 and would adhere to protocol regardless of which arm they were assigned to (see Estimands - non-adherence to protocol section).

Target population: Adjunctive Treatment domain eligible participants who adhere to protocol (see Estimands - non-adherence to protocol section), excluding participants not able to be assessed for adherence from platform entry to day 7 and those with missing mortality status at Day 90, which may be due to participant withdrawal or loss to follow-up.

Endpoint: As for Core Estimand 1.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: Individuals who do not adhere to protocol are excluded from the target population (a principal stratum approach for items IE.1, IE.2 and IE.3), this assumes that treatment allocation does not affect adherence to protocol. Missing endpoint data at Day 90 may

be due to IE.4 or IE.6 and these participants are excluded from the analysis (see target population above).

Sensitivity analyses: None planned.

8.23 Domain-specific Estimand B.2

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause diarrhoea at any time from domain reveal up to 14 days following platform entry, acute hospital discharge, withdrawal or death, whichever occurs first, in platform eligible participants.

Target population: Adjunctive Treatment domain eligible participants excluding those with insufficient data to derive the endpoint.

Endpoint: Three or more loose stools per day, as reported by the patient, a treating nurse or doctor, or reported in medical records any time from domain reveal up to platform day 14 or acute hospital discharge, whichever comes first.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3.

For participants experiencing withdrawal, death or transfer to subsequent acute care site where further clinical data is unavailable (IE.4, IE.5 or IE.6) prior to acute hospital discharge or day 14 (whichever occurs first), their data prior to the intercurrent event (where available) will be used to derive the endpoint; a while-on-treatment strategy).

Sensitivity analyses: None planned.

8.24 Domain-specific Estimand B.3

Objective: To evaluate, within the domain, the effect of revealed randomised intervention compared to the domain control, on the change in blood concentration of C-reactive protein at platform 5 day (+/- 1 day) compared to platform day 1 (day 1 or 24 hours prior), in platform eligible participants.

Target population: Adjunctive Treatment domain eligible participants with available CRP measurements at both platform day 1 (day 1 or 24 hours prior) and day 5 (+/-1 day).

Endpoint: Change in blood concentration of C-reactive protein at platform 5 day (+/- 1 day) compared to platform day 1 (day 1 or 24 hours prior). Platform day 1 CRP is defined as any blood CRP measurement taken on the calendar day of or day before platform entry. Follow up CRP is measured on day 5 (+/-1 day).

Analysis: Continuous endpoint with the general linear function (full details provided in the *SMP* and the *SIG*). Baseline CRP will be included as an additional covariate.

Population level summaries: Mean difference in change score conditional on baseline CRP for intervention compared to domain-control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: Additional anticipated intercurrent events that may occur after platform entry and prior to the Day 5 assessment that may either preclude or effect the endpoint are:
IE B.3.1 - Clinician failure to measure any CRP at platform day 1 or 24 hours prior
IE B.3.2 - Clinician failure to measure CRP post-baseline excluding common intercurrent event reasons IE.4, IE.5. IE.6.

No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3.
Individuals without CRP measured at day 5 (due to IE B.3.2, IE.4, IE.5 or IE.6) will be excluded from the analysis (see target population above). Individuals without CRP measured at platform day 1 (due to IE B.3.1) will be excluded from the analysis (see target population above).
Sensitivity analyses: None planned.

8.25 Domain-specific Estimand B.4

Objective: To evaluate, within the domain, the effect of revealed randomised intervention compared to the domain control, on the probability of a persistent bacteraemia (defined as a positive blood culture) at platform day 5 (+/- 1 day), in platform eligible participants

Target population: Adjunctive Treatment domain eligible participants, excluding participants without an assessment of bacteraemia at day 5 and no evidence of a negative test from day 1-4.

Endpoint: Persistent bacteraemia at day 5 (+/- 1 day) following platform entry. Patients with no test conducted on day 5 (+/-1 day) but with an earlier negative test (on day 1, 2 or 3) will be assigned no persistent bacteraemia at day 5.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3.

Where IE.4, IE.5 and IE.6 occur prior to day 5, where evidence of a negative test is available prior to the intercurrent event, these individuals will be considered to have not met the endpoint (a while on treatment strategy). Where there is no evidence of a negative test these individuals will be excluded from the analysis (see target population).

Sensitivity analyses: None planned.

8.26 Domain-specific Estimand B.5

Objective: To evaluate, within the domain, the effect of revealed randomised intervention compared to the domain control, on the probability of meeting two or more SIRS Criteria simultaneously on day 5 among participants who are alive at day 5.

Target population: Adjunctive Treatment domain eligible participants, excluding participants who have died or withdrawn prior to day 5 or who have missing endpoint data.

Endpoint: Simultaneously, on day 5 following platform entry, meeting two or more of the SIRS Criteria (as defined in the DSA). Where a patient has been discharged home prior to day 5, these individuals will be considered not to have met two or more of the SIRS Criteria.
Analysis: As for Core Estimand 1
Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3.

Where a patient has been discharged home prior to day 5, these individuals are assumed not to have met two or more of the SIRS Criteria and are coded as such, a composite strategy for discharge home prior to day 5. If IE.4, IE.5 or IE.6 have occured prior to day 5 then these individuals are excluded from the analysis (see target population above). Where IE.4, IE.5 or IE.6 occur on day 5 and data are available, a while on treatment strategy will be used.
Sensitivity analyses: None planned.

8.27 Domain-Specific Estimand B.6

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to control, on the probability of acute kidney injury while alive by platform day 14.

Target population: Adjunctive Treatment domain eligible participants, excluding those with end stage kidney disease at baseline and those without creatinine measurements recorded over at least two time windows.

Endpoint: Acute kidney injury between Platform day 1 and Platform day 14. See SNAP Derived Variables (Version 2.0) document for further details.

Analysis: As for Core Estimand 1.

Population level summaries: As for Core Estimand 1.

Intercurrent events strategy: Additional anticipated intercurrent events that may occur after platform entry and prior to the Day 14 assessment that may either preclude or effect the endpoint are:
IE B.1.2.1 - Clinician decision to measure creatinine more frequently than standard care
IE B.1.2.2 - Clinician failure to measure any creatinine at baseline
IE B.1.2.3 - Clinician failure to measure creatinine post-baseline excluding common intercurrent event reasons IE.4, IE.5. IE.6.
No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment

policy strategy for items IE.1, IE.2 and IE.3. No adjustments will be made as a result of additional creatinine measurements; a treatment policy strategy for IE B.1.2.1
For intercurrent events that make measurements impossible (e.g. death) the following strategies will be used:
(i) where death occurs, data prior to death will be used to derive the endpoint; a while alive (while-on-treatment) strategy for IE.5.
(ii) Where some of the data used to calculate the endpoint are missing but could have been measured (the patient is alive at day 14), the following strategies will be used:
- Individuals without creatinine measurement from at least two time periods (due to IE B.1.2.2, IE B.1.2.3, IE.4, IE.6 or discharge home) will be excluded from the analysis (see target population above).
- Individuals with creatinine measurement from only two time periods will have the endpoint derived based on two time periods only.

Sensitivity analyses: None planned.

8.28 Domain-specific Estimand B.7

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to control) on the probability of serious adverse reactions up to 90 days after platform entry.

Target population: Adjunctive Treatment domain eligible participants.

Endpoint: Participants who experience at least one Serious adverse reactions (SAR), defined as any SAE that is suspected to be related (as rated by the treating clinician) to the revealed adjunct-domain intervention in the 90 days following platform entry.

Analysis: No analyses will be performed.

Population level summaries: The frequency and percentage of the endpoint in the Adjunctive arm will be reported.

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. A while-on-treatment strategy is used for withdrawals, death and lost to follow-up (IE.4, IE.5 and IE.6).

Sensitivity analyses: None planned.

8.29 Domain-specific Estimand B.8

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to control on the proportional odds ratio of Desirability Of Outcome Ranking category (DOOR1, modified Antibiotic Resistance Leadership Group version) at platform Day 90.

Target population: Adjunctive treatment domain eligible participants, excluding participants who have a missing DOOR1 score due to withdrawal, loss to follow-up, site personnel or participant availability, or missing diagnostic results or reason for change in revealed domain-specific intervention.

Endpoint: Desirability Of Outcome Ranking category (DOOR1, modified Antibiotic Resistance Leadership Group version), excluding ranking by the modified FBIS score (quality of life) at platform Day 90; change in antibiotics due to inadequate clinical response; and change in antbiotic due to adverse event. As patients in the control arm are unable to receive a ranking of 4 (as an SAR cannot be recorded) rank 3 and 4 will be collapsed into the same category for this endpoint. In the absence of any evidence of a SAR or of an infectious complication, it is assumed that these events have not occurred. Refer to SNAP Derived Variables (Version 2.0) document.

Analysis: Ordinal endpoint modeled using a proportional odds model with a log link function (full details provided in the *SMP* and the *SIG*).

Population level summaries: Conditional log proportional odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1, IE.2 and IE.3. Participants with missing endpoint data, due to any individual sub-component of the endpoint, are excluded from the analysis; this contributes to the definition of the target population and may be due to any combination of withdrawal (IE.4), loss to follow up (IE.6), unavailability of data and non-availability of microbiological testing results due to sample collection, site or laboratory reasons.

Sensitivity analyses: None planned.

8.30 Domain-specific Estimand B.9

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to (flu)cloxacillin (control), on the proportional odds ratio of Desirability Of Outcome Ranking category (DOOR2, SNAP version) at platform Day 90, in adults.

Target population: Adjunctive treatment domain eligible participants, excluding participants who are aged < 18 years or have a missing DOOR2 score due to withdrawal, loss to follow-up, site personnel or participant availability, or missing diagnostic results or reason for change in revealed domain-specific intervention.

Endpoint: Desirability Of Outcome Ranking category (DOOR2, SNAP version), excluding ranking by hospital length of index admission. In the absence of any evidence of a SAR or AE, it is assumed that these events have not occurred. Refer to SNAP Derived Variables (Version 2.0) document.

Analysis: As for Domain-Specific Estimand B.8.

Population level summaries: Conditional log proportional odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone

interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for :

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1 IE.2 and IE.3. In the absence of any evidence of a SAR or adverse safety outcome (including AKI, new RRT days 1-90, persistent RRT at day 90, CDAD, defined in the derived variables document) between days 1-90 after platform entry, it is assumed that these events have not occurred. Participants with missing endpoint data are excluded from the analysis; this contributes to the definition of the target population and may be due to any combination of withdrawal (IE.4), loss to follow up (IE.6), and missing FBIS score at either platform entry or 90 days after platform entry.

Sensitivity analyses: None planned.

8.31 Paediatric and Youth-Specific Estimand 14.P

This may be considered a paediatric variant of core estimand 14, which excludes participants under 18 years of age.

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of return to usual level of function 90 days after platform entry, in platform eligible paediatric participants.

Target population: Adjunctive Treatment domain eligible paediatric participants (aged < 18 years), excluding participants who have missing endpoint data, loss to follow-up or site or participant availability.

Endpoint: Return to usual level of function as reported by carer, 90 days after platform entry.

Analysis: As for Core Estimand 14.

Population level summaries: Conditional log proportional odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: As for core estimand 14.

Sensitivity analyses: None planned.

8.32 Paediatric and Youth-Specific Estimand 15.P

This is now the same as domain-specific estimand B.8 as the previous exclusion of participants < 18 years has been removed and the tie break condition for the DOOR-1 has been removed for the analysis.

8.33 Paediatric and Youth-Specific Estimand 16.P

This may be considered a paediatric variant of original core estimand 16, which has been re-designated as domain-specific estimand B.9, which excludes participants under 18 years of age.

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the proportional odds ratio of Desirability Of Outcome Ranking (DOOR2, SNAP version) at platform Day 90, in platform eligible paediatric participants.

Target population: Adjunctive Treatment domain eligible paediatric participants (aged < 18 years), excluding participants who have a missing DOOR2 score due to withdrawal, loss to follow-up, site personnel or participant availability, or missing diagnostic results or reason for change in revealed domain-specific intervention.

Endpoint: Paediatric Desirability Of Outcome Ranking category (DOOR2, SNAP version), score at platform Day 90, excluding ranking by hospital length of index admission. In the absence of any evidence of a SAR or AE, it is assumed that these events have not occurred. See derived variables document.

Analysis: As for Estimand B.9.

Population level summaries: Conditional log proportional odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: As for Estimand B.9.

Sensitivity analyses: None planned.

8.34 Paediatric and Youth-Specific Estimand P.1

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of any of the four events defined by the composite endpoint occurring.

Target population: Adjunctive Treatment domain eligible paediatric participants excluding participants with incomplete evidence to construct the composite endpoint. See SNAP Derived Variables (Version 2.0) for further details.

Endpoint: Paediatric composite outcome, considered to have occurred if any of the following events have occurred:
1. Mortality by day 90 following platform entry
2. Microbiological treatment failure defined as positive sterile site culture for S. aureus (of the same silo as the index isolate) between 15 and 90 days after platform entry
3. Diagnosis of new foci between 15 and 90 days after platform entry
4. Length of total index hospitalisation of > 30 days from the time of platform entry. Total index hospitalisation is defined as a continuous admission to any healthcare facility, including rehabilitation hospitals, and hospital-in-the-home or outpatient parenteral antimicrobial therapy services.

See SNAP Derived Variables (Version 2.0) for further details.

Analysis: As for Core Estimand 1.

Population level summaries: Conditional odds ratio of the endpoint for intervention compared to control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain adults (Clindamycin vs no adjunctive treatment).
- Adjunct-domain paediatrics (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1 IE.2 and IE.3. As for estimands 1, 10 and 11 for the derivation of the mortality, microbiological failure and new foci components of the composite treatment failure. In addition, missing endpoint data for length of total index hospitalisation within platform days 1-30 may be due to IE.4 or IE.6 (e.g. transfered to acute care not registered as a SNAP site). Participants with missing data for any event (either mortality, microbiological treatment failure, diagnosis of new foci or hospital stay greater than 30 days) will be excluded from the target population (i.e. will have a missing endpoint), unless there is affirmative evidence of meeting the endpoint from any of the other events.

Sensitivity analyses: None planned.

8.35 PWID Estimand PWID.1

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of patient directed discharge while on-treatment in participants identifying as PWID.

Target population: Adjunctive Treatment domain eligible adult-PWID participants.

Endpoint: Patient directed discharge. See SNAP Derived Variables (Version 2.0) for further details.

Analysis: As for Core Estimand 1.

Population level summaries: Conditional log odds ratio of the endpoint for intervention compared to domain-control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain PWID adults (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1 IE.2 and IE.3. Where death, withdrawal or discharge to subsequent acute care site occurs and further clinical data is unavailable, data prior to the event will be used similar to a while-on-treatment strategy for IE.4, IE.5 and

IE.6, i.e. where a death or withdrawal occurred in acute care this patient's outcome would be no patient directed discharge. Participants with missing endpoint data are excluded from the analysis; this contributes to the definition of the target population and will be addressed in the sensitivity analysis.

Sensitivity analyses: The analysis may be repeated with up to two different assumptions pertaining to individuals with unknown mortality status at day 90:

- Sensitivity estimand PWID.1.1: Anyone with a discharge without knowledge of patient directed discharge or not will be assumed to have undergone a patient directed discharge, a composite strategy for failure to capture data.
- Sensitivity estimand PWID.1.2: Anyone with a discharge without knowledge of patient directed discharge or not will be assumed to have not undergone a patient directed discharge, a composite strategy for failure to capture data.

The analysis that favours the control arm (no adjunctive treatment) will be considered the key sensitivity estimand.

8.36 PWID Estimand PWID.2

Objective: To evaluate, within the domain, the effect of revealed randomised interventions compared to the domain control, on the probability of readmission to hospital within 90 days of platform entry in participants identifying as PWID.

Target population: Adjunctive Treatment domain eligible adult-PWID participants excluding individuals who reside in jurisdictions where data linkage could not be performed.

Endpoint: Readmission to hospital after discharge (self or planned) within 90 days after platform entry. See SNAP Derived Variables (Version 2.0) for further details.

Analysis: As for Core Estimand 1.

Population level summaries: Conditional log odds ratio of the endpoint for intervention compared to domain-control groups, adjusted for potential interaction with MRSA backbone interventions (which cannot be reported until the MRSA domain reaches a conclusion to maintain trial integrity) estimated for:

- Adjunct-domain PWID adults (Clindamycin vs no adjunctive treatment).

Intercurrent events strategy: No adjustments will be made to the endpoint or the analysis as a result of permanently or temporarily stopping the intervention due to tolerance, efficacy, adherence or adverse events; a treatment policy strategy for items IE.1 IE.2 and IE.3. Where data linkage could not be performed the endpoint is unavailable, this is reflected in the target population.

Sensitivity analyses: None planned.

9 Pre-specified Subgroup Analyses

The primary statistical model includes adult and paediatric subgroups and domain efficacy is assessed separately for these subgroups after accounting for data-driven information sharing between them. Further subgroups are pre-specified in the core protocol and appendices for the primary endpoint only. Separately, for each set of mutually exclusive subgroups defined below, paediatric and

adult data will be pooled and the analysis will include data-driven information sharing (borrowing) between the subgroups.

- 1. *Clindamycin resistance:* subgroups are defined as no resistance, inducible resistance, constitutive resistance. $U \in$ {None, Inducible, Constitutive }
- 2. *Severe disease phenotype:* subgroups are defined as ICU/HDU admission at the time of platform entry and no ICU/HDU admission at the time of platform entry. $U \in$ {ICU/HDU admission, no ICU/HDU admission}
- 3. *Panton valentine leucocidin (PVL) positive isolate:* subgroups are defined as PVL positive isolate and PVL negative isolate. $U \in$ {PVL positive, PVL negative }
- 4. *Antibiotic susceptibility silo:* Subgroups are defined as PSSA silo, MSSA silo, MRSA silo. $U \in$ {PSSA, MSSA, MRSA}. Note that this subgroup analysis was not specified in the core protocol or appendices.

The exception is the following analysis, which retains a mutually exclusive paediatric subgroup in addition to the division of the adult cohort into people who do and do not inject drugs. This analysis will include data-driven information sharing (borrowing) between these subgroups.

- 5. *People who inject drugs (PWID) :* subgroups defined as adult-person-who-injects-drugs, adult-person-who-does-not-inject-drugs and paediatric. $U \in$ {Adult PWID, Adult non-PWID, Paediatric}.

The following subgroups will only be reported descriptively:

- 6. *Pregnancy :* simple summary statistics and listings will be generated for pregnant participants.
- 7. *Ethnicity :* subgroups for populations of special interest (as requested by funding agencies) are defined as maori, south-pacific-islander and non-maori-or-south-pacific-islander. Further subgroups by ethnicity may also be requested and similarly analysed and reported.

For subgroup analyses 1 through 5 the population summary of the primary estimand (log odds ratio of mortality by Day 90 for intervention compared to control) will be estimated separately for each subgroup. The primary statistical model will be expanded to incorporate the additional model parameters required to incorporate the expansion of the number of subgroups, namely $\alpha_{s,u}$, $\beta_{s,u,d_{kj}}$ and $\psi_{s,u,d_{kj},d_{kl}}$. For example, for the analysis of clindaymycin resistance, three subgroups will specified in the subgroup parameter such that $U = \{1, 2, 3\} \rightarrow$ {no resistance, inducible resistance, constitutive resistance}. Outputs of these models will be reported in the same manner as the primary model reports the primary subgroups (adults/paediatrics). The subgroup specific log-odds ratio is modelled as normally distributed with an intervention-specific mean and variance:

- $\beta_{u,d_{kj}} \sim N(\mu_{u,d_{kj}}, \tau^2_{d_{kj}})$
- $\mu_{d_{kj}} \sim N(0, 1^2)$
- $\tau_{d_{kj}} \sim IG(1, 0.0625)$

All categories for a defined subgroup are mutually exclusive, but in some cases a category may have low or zero frequencies; in these situations the model parameters may be collapsed to account for sparse data.

For subgroup analysis 6 (pregnancy), relevant outcomes (see SNAP Pregnancy-Specific Appendix) will be presented for members of the pregnant subgroup in a table. Note that pregnant

participants are provided with the choice to consent to the collection of additional (pregnancy-specific) data, all pregnant participants will be included in the pregnancy cohort and footnotes will be included in the summaries to indicate the number of participants who did not consent to pregnancy-specific data collection to account for missingness.

For subgroup analysis 7 (ethnicity) - mortality by day 90 for participants assigned to intervention; and for participants assigned to control will be summarised as frequency (%) and reported separately for each ethnicity within each country. Where multiple ethnicity categories have been selected by a participant (maximum of two permissible), the following rules will be applied in priority order for report summaries:

1. Any combination with Maori peoples classified as Maori
2. Any combination with Pacific Islander peoples classified as Pacific Islander
3. Any combination with First Nation peoples (Indigenous) classified as Indigeneous
4. Any combination with Jewish peoples classified as Jew
5. Any combination with Black peoples classified as Black
6. Any combination with Hispanic or Latino peoples classified as Hispanic/Latino
7. Any combination with Asian peoples classified as Asia
8. Any combination with South/South East Asia peoples classified as South/South East Asian
9. Any combination with Middle Eastern and Arabian peoples classified as Middle Eastern
10. Any combination with White or European peoples classified as White

10 SAP specified estimands

There are no additional estimands specified in this SAP.

11 Post hoc analyses

Estimands and analyses for the adjunctive domain are classified as post-hoc if they are defined after the date of data transfer for the first report arising from this SAP. The results from these analyses will be clearly labeled and reported as post-hoc in any reports and arising publications.

12 Safety events defined for DSMC reports

The following safety events have been defined for DSMC open and closed reports:

- C. difficile (derived)
- C. difficile (reported)
- C. difficile (total)
- Acute Kidney Injury (derived day 1-14)
- Acute Kidney Injury (reported to day 90)
- Acute Kidney Injury (total)
- Hepatotoxicity (derived)
- Hepatotoxicity (reported)
- Hepatotoxicity (total)

The definitions (accounting for incomplete and missing data and accounting for additional levels of stratification) of these safety events and denominators are similar to the approach used by the analytic team for the preparation of the 8th interim analysis (conducted on the 16th June 2025) and are detailed in the *SNAP Derived Variables (Version 2.0)* document. These data will be presented in a descriptive table with frequencies, participant denominators and percentages by silo-specific intervention group.

13 Acute Kidney Injury Staging

The derived Acute Kidney Injury staging (no acute kidney injury, stage 1 acute kidney injury, stage 2 acute kidney injury and stage 3 acute kidney injury) will be presented in a descriptive table with frequencies, participant denominators and percentages by silo-specific intervention group.

14 Deviations from the protocol

Deviations from the protocol are routinely reviewed by the DSMC in the closed report. The free text in these closed reports has the potential to unblind readers of the current report and, therefore, will not be reported.

15 Derived variables

Derived variables are defined in the SNAP Derived Variables (Version 2.0) document.

16 Efficacy analyses

The analyses for the SNAP estimands are defined in generic terms in the statistical appendix to the protocol and the SMP, and in more detail for the parameters of the linear function and decision criteria in the SIG. It was noted that the general linear function parameters for ineligibility to the SNAP domains were mis-specified as γ_{D_k} in the SMP, whereas the statistical appendix to the protocol defines these as $\gamma_{a,s,D}$, where a denotes the subgroup, s denotes the silo and D denotes the domain. The parameterisation defined for domain ineligibilities from the statistical appendix is used for all analyses, unless stated otherwise in the SAP.

This section provides details for any sensitivity analyses, sub-study analyses and country-specific analyses.

16.1 Sub-study analyses

None defined for the Analytic Team.

16.2 Country-specific analyses

A pre-specified subgroup analysis of Estimand 1 for NZ will be performed, using NZ ethnic categories of Maori, South Pacific Islanders and pooling the other NZ ethnic groups (see section on *Pre-specified subgroup analyses* above). This is required to estimate the Estimand 1 population level summaries in these ethnic groups.

17 Reporting

17.1 General summaries

Continuous variables will be summarised using mean (standard deviation) for symmetric distributions and median (IQR) for asymmetric distributions. Categorical (including ordinal and binary) variables will be summarised using frequency (percentage) for each level.

17.2 Presentation of country-specific summaries

For all countries, the eligible adult population will be summarised for each endpoint with respect to ethnicity (i.e. not further broken down by backbone interventions).

17.3 Presentation of population-level summaries

Posterior distributions will be summarised and reported using medians and 95% equal-tailed credible intervals. Model posteriors will also be presented graphically.

17.4 Presentation of decision criteria

Non-inferiority and futility of non-inferiority will be reported as posterior probabilities according to the decision criteria defined in the SIG. In addition, further reporting requirements may also be specified in the estimands.

17.5 Presentation of safety data

Serious Adverse Reactions (SARs) (excluding deaths) possibly, probably, or definitely related to adjunctive domain interventions will be reported using descriptive summaries by silo-specific intervention group and overall in a summary table at the MedDRA preferred term level.

Serious Adverse Events (SAEs) are recorded in selected countries due to regulatory requirements. These are routinely provided to the DSMC and will not be reported.

Safety events defined for the DSMC will also be presented in a descriptive table with frequencies, participant denominators and percentages .

17.6 Presentation of concurrent medications

Concurrent medications will not be reported in order to maintain trial integrity.