SNAP Statistical Implementation Guide

Version 9.0

28 August 2025

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Versions

Version 0.1

Initial draft developed by the SNAP Analytic Team prior to being unblinded.

Version 1.0

Version 1.0 for scheduled analysis 1. Unchanged from version 0.1, except:

- amendment of label for Methicillin-resistant S.aureus (changed from PSSA to MRSA) and clarification of intervention identifiers in section 2.2
- includes dates of the data cut for scheduled analysis 1 and subsequent DSMC meeting;
- further clarification of intervention identifiers for decision quantities in section 5.2 and representation of decision rules on the untransformed scale.

Version 2.0

Version 2.0 for scheduled analysis 2. Unchanged from version 1.0, except:

- includes dates of the data cut for scheduled analysis 2 and subsequent DSMC meeting.

Version 3.0

Version 3.0 for scheduled analysis 3. Unchanged from version 2.0, except:

- includes dates of the data cut for scheduled analysis 3 and subsequent DSMC meeting;
- includes further dates defining the epochs (derived by the analyst).

Version 4.0

Version 4.0 for scheduled analysis 4. Unchanged from version 3.0, except:

- includes dates of the data cut for scheduled analysis 4 and subsequent DSMC meeting.

Version 5.0

Version 5.0 for scheduled analysis 5. Unchanged from version 4.0, except:

- includes dates of the data cut for scheduled analysis 5 and subsequent DSMC meeting;
- includes information on subpopulations, including definition of adults and children;
- includes external factors and feedback from the SNAP DSMC concerning suspension of backbone PSSA/MSSA silos for adults;
- clarifies inclusion of sites in CONSORT flowcharts for adults and paediatrics;
- corrects list of analyses and summaries performed at each scheduled analysis.

Version 6.0

Version 6.0 for scheduled analysis 6. Unchanged from version 5.0, except:

- includes dates of the data cut for scheduled analysis 6 and subsequent DSMC meeting;
- clarifies status of interventions within each domain by subgroup (adults and paediatrics);
- includes brief details indicating that an open DSMC report is generated.

Version 7.0

Version 7.0 for scheduled analysis 7. Unchanged from version 6.0, except:

- includes dates of the data cut for scheduled analysis 7 and subsequent DSMC meeting;
- includes updates to notes in Trial Status section to improve clarity;
- includes a statement in the reporting section confirming that for the DSMC closed reports from the scheduled; analyses, parameter estimates and decision quantities, including summaries and/or graphical representations, will not be reported for closed domains or silos or subgroups (as appropriate) after the last recruited participant for the closed domain/silo/subgroup has completed follow-up, unless stated otherwise in the current version of the SIG.

Version 8.0

Version 8.0 for scheduled analysis 8. Unchanged from version 7.0, except:

- includes dates of the data cut for scheduled analysis 8 and subsequent DSMC meeting;
- includes updates to active domains and new countries that have commenced recruitment.

Version 9.0

Version 9.0 for scheduled analysis 9. Unchanged from version 8.0, except:

- includes dates of the data cut for scheduled analysis 9 and subsequent DSMC meeting;
- includes updates to active domains and new countries that have commenced recruitment;
- removed section 2.7 as information on adult and paediatric subgroups now included in sections 2.3 to 2.6
- defines models with constrained parameters for each domain to account for post randomisation events (i.e. eligibility for other domains that are assessed after the start of the intervention), closure of domains and eligibility restrictions by subgroup (e.g. children are excluded in PET/CT domain).

1 Introduction

The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Statistical Implementation Guide (SIG) supplements the SNAP Statistical Appendix. Whereas the SNAP Statistical Appendix prescribes the SNAP trial analyses in general, the SIG provides additional explanation regarding the trial status and specific analytical approaches that should be implemented at a scheduled analysis. While the SNAP Statistical Appendix is a largely immutable document that requires ethics approval to be modified, the SIG is updated for each scheduled analysis by the Statistical Subcommittee, and pushed to a GitHub repository as a specific release.

The purpose of the SIG is to, at each scheduled analysis:

1. summarise the trial status
2. instruct analysts in terms of specific modelling requirements

The production of SIG version 5.0 was delayed until 16 August 2024 to confirm the decisions of the GTSC following recomendations provided by the SNAP DSMC on 6 August 2024. The analyses and summaries remain unchanged from SIG version 4.0 but additional detail is provided on the recruitment status of the subgroups (as documented in the version history).

2 Trial status

All dates in this document refer to Australian Eastern standard time (AEST), although data is recorded relative to local time cross the countries and regions.

2.1 Key dates

Table 1: Key analytical events

Event	Date	Notes
Recruitment opens	16 Feb 2022	–
Scheduled analysis 9		
- Data cutoff	13 Aug 2025	–
- Data available	27 Aug 2025	–
- Report due to DSMC	24 Sep 2025	–
- DSMC meeting proposed	by 08 Oct 2025	–

2.2 Domains

At the time of writing, the following domains are either currently available, being planned or have previously been available:

1. Backbone antibiotic domain, comprising the:
    - Methicillin-susceptible *S. aureus* (MSSA) silo
    - Penicillin-susceptible *S. aureus* (PSSA) silo
    - Methicillin-resistant *S. aureus* (MRSA) silo
2. Adjunctive antibiotic domain
3. Early oral switch (EOS) domain
4. PET-CT domain

The following tables summarise the current domain status. The following definitions apply:

- **Open**: domain/intervention is active and recruiting
- **Paused**: domain/intervention is active but not recruiting
- **Closed**: domain/intervention is no longer active (i.e. permanently closed)
- **Pending**: domain being developed for future enrolments (for information only)

Table 2: Domain status

Domain	Status	Open date	Stop date	Notes
Backbone antibiotic				
- MSSA	Open	16 Feb 2022	–	Closed for adults 21 Jun 2024, remains open for paediatrics
- PSSA	Open	16 Feb 2022	–	Closed for adults 21 Jun 2024, remains open for paediatrics
- MRSA	Open	16 Feb 2022	–	–
Adjunctive antibiotic	Closed	16 Feb 2022	16 Jul 2025	Closed for adults and paediatrics on 16 Jul 2025
Early oral switch	Open	16 Feb 2022	–	Closed for paediatrics 19 Feb 2025, remains open for adults
PET-CT	Open	15 Aug 2024	–	–

2.3 Backbone antibiotic interventions

Table 3: Backbone antibiotic status

Intervention	Subgroup	Status	Open date	Stop date	Notes
MSSA					
- Flucloxacillin (d_{11})	Adult	Stopped	16 Feb 2022	21 Jun 2024	Advice from DSMC
	Paed.	Open	16 Feb 2022	–	Paused from 21Jun2024 until 11Mar2025
- Cefazolin (d_{12})	Adult	Stopped	16 Feb 2022	21 Jun 2024	Non-inferiority met
	Paed.	Open	16 Feb 2022	–	Paused from 21Jun2024 until 11Mar2025
PSSA					
- Flucloxacillin (d_{11})	Adult	Stopped	16 Feb 2022	21 Jun 2024	Advice from DSMC
	Paed.	Open	16 Feb 2022	–	Paused from 21Jun2024 until 11Mar2025
- Penicillin (d_{13})	Adult	Stopped	16 Feb 2022	21 Jun 2024	No comparator

Intervention	Subgroup	Status	Open date	Stop date	Notes
	Paed.	Stopped	16 Feb 2022	21 Jun 2024	Decision on 4Sep2024 to switch to cefazolin
- Cefazolin (d_{12})	Paed.	Open	11 Mar 2025	–	–
MRSA					
- Vancomycin (d_{14})	Adult	Open	16 Feb 2022	–	–
	Paed.	Open	16 Feb 2022	–	–
- Vancomycin + cefazolin (d_{15})	Adult	Open	16 Feb 2022	–	–
	Paed.	Open	16 Feb 2022	–	–

2.4 Adjunctive antibiotic interventions

Table 4: Adjunctive antibiotic status

Intervention	Subgroup	Status	Open date	Stop date	Notes
No clindamycin (d_{21})	Adult	Closed	16 Feb 2022	16 Jul 2025	–
	Paed.	Closed	16 Feb 2022	16 Jul 2025	–
Clindamycin (d_{22})	Adult	Closed	16 Feb 2022	16 Jul 2025	–
	Paed.	Closed	16 Feb 2022	16 Jul 2025	–

2.5 Early oral switch domain

Table 5: Early oral switch status

Intervention	Subgroup	Status	Open date	Stop date	Notes
Usual care (d_{31})	Adult	Open	16 Feb 2022	–	–
	Paed.	Stopped	19 Feb 2025	11 Mar 2025	–
Early oral switch (d_{32})	Adult	Open	16 Feb 2022	–	–
	Paed.	Stopped	19 Feb 2025	11 Mar 2025	–

2.6 PET-CT domain

Table 6: PET-CT status

Intervention	Subgroup	Status	Open date	Stop date	Notes
Usual care	Adult	Open	15 Aug 2024	–	–
	Paed.	Not elig.	–	–	Ineligible
Intervention	Adult	Open	15 Aug 2024	–	–
	Paed.	Not elig.	–	–	Ineligible

3 Planned analysis

3.1 Analyses

Planned analyses are summarised below. Details of the estimands for the Core Protocol can be found in the Statistical Appendix. Details for the domain-specific appendices estimands can be found within the relevant domain-specific appendix.

Estimand	Type	Subset	Outcome	Model	Notes
Core 1	Primary	All	90-day mortality	Binary	-
Core 12	Secondary	Backbone PSSA/MSSA/MRSA	C.difficile diarrhoea (upto day 90)	None	Summarised only
A1.2,A2.2	Secondary	Backbone PSSA/MSSA/MRSA	Acute kidney injury (AKI)	None	Summarised only
A1.5	Secondary	Backbone PSSA/MSSA	Hepatotoxicity (Acute liver injury, ALI)	None	Summarised only
A1.7,A2.8	Secondary	Backbone PSSA/MSSA/MRSA	Change in assigned treatment (index hospitalisation)	None	Summarised only
Core 13	Secondary	All	SARs (not SAEs)	None	Summarised only

3.2 Included variables

See SNAP Statistical Appendix for modelling details.

3.2.1 Eligibility

Currently, eligibility (to be randomised) is modelled for all three domains (backbone, adjunctive, and early-oral switch domains). Ineligibility could be for any reason (for participants in the platform) including site unavailability, non-consent or, as in the early-oral switch domain, failure to qualify for randomisation to a domain.

3.2.2 Interactions

Table 7: Included interactions

Silo	Domains	Status	Open date	Stop date	Notes
MRSA	Backbone, Adjunctive	Open	16 Feb 2022	–	

3.2.3 Regions

Regions are included in the current model (see below). Note that where a region contains less than 5 observations, it may be combined with the most relevant neighbouring region at the analysts discretion.

Note that the `region` variable is not collected and must be derived and assigned by the analyst.

Table 8: Included regions

Region	Status	Open date	Stop date	Notes
Africa and the Middle East (ex. Israel)	Open	21 Aug 2023	–	–
East Asia	Open	18 Jul 2025	–	–
Europe (inc. Israel & Sweden)	Open	14 Dec 2022	–	–
Oceania	Open	16 Feb 2022	–	–
North America	Open	01 Apr 2022	–	–
South and Central America	–	–	–	–
South-east Asia	Open	24 Nov 2022	–	–
South Asia	–	–	–	–

3.2.4 Countries

Countries are included (see below), nested within regions (see above) within the current model. Note that where a country contains less than 5 observations, it may be combined with the most relevant country within the nesting region (if possible), at the analysts discretion.

Note that the `region` variable is not collected and must be derived and assigned by the analyst.

Table 9: Included countries

Country	Region	Status	Open date	Stop date	Notes
Australia	Oceania	Open	16 Feb 2022		
Canada	Nth America	Open	01 Apr 2022	–	
Germany	Europe	Open	01 Mar 2025	–	
Israel	Europe	Open	14 Dec 2022	–	
Japan	East Asia	Open	18 Jul 2025	–	
Netherlands	Europe	Open	26 Oct 2023	–	
New Zealand	Oceania	Open	20 Feb 2022	–	
Singapore	SE Asia	Open	24 Nov 2022	–	
South Africa	Africa & M.East	Open	21 Aug 2023	–	
Sweden	Europe	Open	01 Mar 2025	–	
United Kingdom	Europe	Open	27 Nov 2023	–	

3.2.5 Covariates

Age group is included as a covariate within the current model (see below). Note that where an age group contains less than 5 observations, it may be combined with the most relevant neighbouring category at the analysts discretion.

Note that the age group variable is not collected and must be derived by the analyst.

Table 10: Included covariates

Covariate	Levels	Notes
Age group	30 days or less	
	31–365 days	
	1–4 years	
	5–11 years	
	12–17 years	
	18–39 years	
	40–59 years	
	60–79 years	
	80 years and over	

3.2.6 Epochs

Note that the epoch variable is not collected and must be derived by the analyst.

Table 11: Included epochs

Epoch	Notes
16 Feb 2022–17 Aug 2022	
18 Aug 2022–15 Feb 2023	
16 Feb 2023–17 Aug 2023	
18 Aug 2023–15 Feb 2024	
16 Feb 2024–17 Aug 2024	
18 Aug 2024–15 Feb 2025	
16 Feb 2024–17 Aug 2025	

4 Model implementation

4.1 Posterior computation

The posterior distributions of all models described in section 3.1 will be computed using Markov chain Monte Carlo (MCMC) methods via Stan. Convergence and mixing of chains must be assessed using standard diagnostics including, but not limited to, graphical inspection of the chains, and ensuring all $\hat{R}$ values are close to one. Posterior predictive distributions should be examined against the observed data, where possible, to evaluate the suitability of the proposed models.

4.2 Model code

The analyses specified in section 3.1 will be performed using Stan, impemented in the R programming environment. A snapshot of the R environment must be included along with any report. The following domain-specific model parameter restrictions will be imposed :

4.3 Model deviations

All models and priors are specified in the Statistical Appendix. In the event that the pre-specified models do not converge or other modelling issues are encountered (e.g. divergent transitions in the Stan sampler), the analyst may choose to modify the model in order to proceed. Any and all deviations from the pre-specified model must be detailed along with the reported results.

Modelling issues have been encountered as the SNAP platform has matured and adaptations have occurred to the domains or the population subgroups. To address these issues domain-specific models are defined below, which are nested in the overarching SNAP statistical model.

Backbone domain

As per the SNAP statistical model but constraining the following parameters to zero (dropping model parameters):

- eligibility parameters ($\gamma_{D_{s(i),u(i),k(i)}}$) for EOS and PET/CT domains
- intervention parameters ($\beta_{s(i),u(i),d_{kj(i)}}$) for EOS and PET/CT domains

Adjunctive domain

As per the SNAP statistical model but constraining the following parameters to zero (dropping model parameters):

- eligibility parameters ($\gamma_{D_{s(i),u(i),k(i)}}$) for EOS and PET/CT domains
- intervention parameters ($\beta_{s(i),u(i),d_{kj(i)}}$) for EOS and PET/CT domains

Early oral switch domain

As per the SNAP statistical model but excluding the data from paediatric participants and constraining the following parameters to zero (dropping model parameters):

- intercept parameters ($\alpha_{s(i),u(i)}$) for paediatric subgroup
- eligibility parameters ($\gamma_{D_{s(i),u(i),k(i)}}$) for paediatric subgroup and for PET/CT domain
- intervention parameters ($\beta_{s(i),u(i),d_{kj(i)}}$) for paediatric subgroup and for PET/CT domain

PET/CT domain

As per the SNAP statistical model but excluding the data from paediatric participants and constraining the following parameters to zero (dropping model parameters):

- intercept parameters ($\alpha_{s(i),u(i)}$) for paediatric subgroup
- eligibility parameters ($\gamma_{D_{s(i),u(i),k(i)}}$) for paediatric subgroup and for EOS domain
- intervention parameters ($\beta_{s(i),u(i),d_{kj(i)}}$) for paediatric subgroup and for EOS domain

5 Reporting

For the DSMC closed reports from the scheduled analyses, parameter estimates and decision quantities, including summaries and/or graphical representations, will not be reported for closed domains or silos or subgroups (as appropriate) after the last recruited participant for the closed domain/silo/subgroup has completed follow-up, unless stated otherwise in the current version of the SIG.

5.1 Posterior summaries

Model posteriors will be summarised and reported using mean, median, and 95% equal-tailed credible intervals. Treatment odds ratios will be reported in terms of decision rules.

5.2 Decision rules

Posterior probabilities of treatment efficacy will be summarised as described below (see 'Quantity'). Quantities are defined for silo (1=MSSA, 2=PSSA, 3=MRSA), subgroup (adult=1, child=0), and intervention within a domain are defined in section 2.2. Whether a decision rule is met must be based on the corresponding threshold, and this should be reported. Note that the same decision criteria may be appropriate for the paediatric subgroup but currently no decision criteria are defined for this subgroup.

Table 12: Backbone domain decision rules

Silo	Intervention	Decision	Quantity	Threshold
MSSA	Cefazolin	Non-inferiority	$P(exp(\beta_{1,1,d_{12}}) < 1.2)$	> 0.99
		Futility (ninf)	$P(exp(\beta_{1,1,d_{12}}) < 1.2)$	< 0.01
PSSA	Penicillin	Non-inferiority	$P(exp(\beta_{2,1,d_{13})} < 1.2)$	> 0.99
		Futility (ninf)	$P(exp(\beta_{2,1,d_{13}}) < 1.2)$	< 0.01
MRSA	Vancomycin + cefazolin	Superiority	$P(exp(\beta_{3,1,d_{15}}) < 1)$	> 0.99
		Futility (sup)	$P(exp(\beta_{3,1,d_{15}}) < 1/1.2)$	< 0.01

Table 13: Adjunctive domain decision rules

Silo	Intervention	Decision	Quantity	Threshold
All	Clindamycin	Superiority	$P(exp(\beta_{1,1,d_{22}}) < 1)$	> 0.99
		Futility (sup)	$P(exp(\beta_{1,1,d_{22}}) < 1/1.2)$	< 0.01

Table 14: Early-oral switch domain decision rules

Silo	Intervention	Decision	Quantity	Threshold
MSSA	Early-oral switch	Non-inferiority	$P(exp(\beta_{1,1,d_{32}}) < 1.2)$	> 0.99
		Futility (ninf)	$P(exp(\beta_{1,1,d_{32}}) < 1.2)$	< 0.01
PSSA	Early-oral switch	Non-inferiority	$P(exp(\beta_{2,1,d_{32}}) < 1.2)$	> 0.99
		Futility (ninf)	$P(exp(\beta_{2,1,d_{32}}) < 1.2)$	< 0.01
MRSA	Early-oral switch	Non-inferiority	$P(exp(\beta_{3,1,d_{32}}) < 1.2)$	> 0.99
		Futility (ninf)	$P(exp(\beta_{3,1,d_{32}}) < 1.2)$	< 0.01

5.3 Response adaptive randomisation

Response adaptive randomisation is not planned at this stage.

5.4 Reports produced

The analytic team will provide an open report to the DSMC summarising information, without any indication of allocated interventions, on trial recruitment, monitoring of adherence to protocol, data quality and safety. A closed report will also be provided, describing results in terms of the unblinded treatment allocations, to the data safety and monitoring committee only by the analytic team. At no point should any blinded trial investigators orresearch personnel be able to access the closed report.