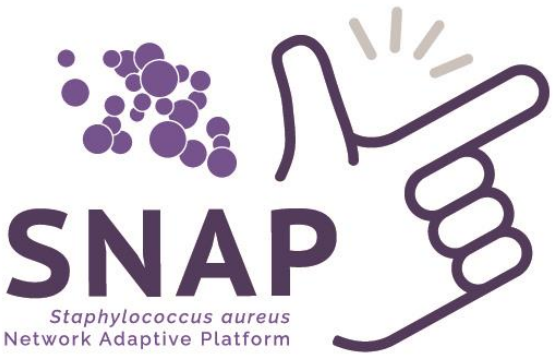

Statistical Analysis Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Statistical Analysis Appendix Version 2.0 dated 24 March 2023

Summary

The focus of this Statistical Analysis Appendix is to describe the statistical methods and decision criteria for making trial adaptations, recommending domain- or cell-specific conclusions for non-inferiority, superiority or futility compared to control, and reporting final domain analyses for the SNAP trial. It draws on information in the core SNAP protocol and domain specific appendices to define platform and domain objectives, target populations, endpoints, statistical methods and models and population level estimators within the estimand framework. It provides a technical bridge between the core protocol, domain specific appendices and the statistical implementation guide.

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1. ABBREVIATIONS

AE	Adverse event
AKI	Acute Kidney Injury
AR	Adverse reaction
ASID CRN	Australasian Society for Infectious Diseases Clinical Research Network
ASP	Antistaphylococcal Penicillin
CPI	Coordinating Principal Investigators
CRF / eCRF	Case Report Form / Electronic Case Report Form
CTMS	Clinical Trial Management System
DSMC	Data and Safety Monitoring Committee
DSA	Domain Specific Appendix
DSWG	Domain Specific Working Group
GTSC	Global Trial Steering Committee
GCP	Good Clinical Practice
HITH	Hospital in the home
HREC	Human Research Ethics Committee
ICMJE	International Committee of Medical Journal Editors
ID physician	Infectious Disease physician
IDSA	Infectious Diseases Society of America
IIG	International Interest Group
IPCW	Inverse Probability of Censoring Weights
IQR	Interquartile range
ITT	Intention-to-treat
MCMC	Markov Chain Monte Carlo
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NHMRC	National Health and Medical Research Council
OPAT	Outpatient Parenteral Antimicrobial Therapy
PSSA	Penicillin-Susceptible *Staphylococcus aureus*
PWID	People Who Inject Drugs
QoL	Quality of Life
RAR	Response Adaptive Randomisation
RCT	Randomised Control Trial
REMAP	Randomised Embedded Multifactorial Adaptive Platform
RSA	Region Specific Appendix
RTSC	Regional Trial Steering Committee
SAB	*Staphylococcus aureus* Bacteraemia
SIG	Statistical Implementation Guide (current state of the analytic plan based on any previous platform adaptations)
SNAP-SS	SNAP Statistical Subcommittee
SNAP	*Staphylococcus aureus* Network Adaptive Platform trial
SOP	Standard Operating Procedures

2. GLOSSARY

Acute index hospitalisation	Initial hospital admission to an acute inpatient facility, this does not include HITH/OPAT/COPAT and stepdown inpatient rehabilitation/post-acute care
Core Protocol	A core or master protocol is defined as a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate one or more investigational drugs or interventions, in one or more disease subtypes within the overall trial structure. The SNAP core protocol has multiple interventions and drug combinations for three subtypes of *Staphylococcus aureus* bacteraemia (PSSA, MSSA & MRSA).
Cell	A combination of a domain and a silo will be known as a “cell”. For the backbone domain, there are 3 different cells. For the clindamycin and early oral switch domain, there is only one cell in each (i.e., all 3 silos will have the same interventions available to be randomised to).
Domain	A domain is a group of interventions with comparable modes of action or contexts of care for which there exists clinical equipoise. For example, backbone antibiotic or early oral switch.
Domain-Specific Appendix	A domain-specific appendix is defined as a sub-protocol that is embedded within the trial structure of the core protocol and addresses research question(s) and objective(s) within a particular field of care, in one or more disease subtypes.
Estimand	An estimand is a detailed description of the treatment effect of interest in a clinical trial. It is a combination of eligibility (inclusion, exclusion criteria applied to the population of interest), endpoint or outcome definitions, description of treatment arms, the statistical analysis applied, management of post-randomisation events (e.g. adherence issue, non-compliance, missing or unreported data, missed assessments) and population level summaries or effect sizes.
Platform	Participants in the platform are those who meet all core eligibility criteria and consent to inclusion in the platform. Occasional participants in the platform will not receive any randomised intervention (if they are not eligible for any available domain).
Platform Entry	“Platform entry” is defined as the timepoint when the participant has met core eligibility criteria, given informed consent for the platform, and been randomised.
Platform Trial	A "platform trial" is a clinical trial with a single core protocol in which

	multiple treatments or interventions are evaluated simultaneously. Participants in the SNAP platform are those who meet all core eligibility criteria and consent to inclusion in the platform. Occasional participants in the platform will not receive any randomised intervention (if they are not eligible for any available domain).
Randomised Embedded Multifactorial Adaptive Platform	REMAPs combine features of adaptive platform trials with pragmatic point-of-care trials to determine best treatment strategies for participants. The designs have four key features: 1) randomisation, allowing robust causal inference; 2) embedding of study procedures into routine care processes, facilitating enrolment, trial efficiency, and generalisability; 3) a multifactorial statistical model comparing multiple interventions across multiple participant subgroups; and 4) an adaptive platform structured to permit continuous, potentially perpetual enrolment beyond the evaluation of the initial treatments.
Regimen	A regimen refers to the combination of interventions an individual is allocated to receive. Initially, for sites that do not opt out of any domains, for each silo there are eight potential regimens.
Registry	Participants in the registry include all those in the platform (as defined above) PLUS the “registry only” participants. Registry only participants are those who are not in the platform, but who have consented to being in the registry.
Silo	Subgroups of participants defined by the antibiotic susceptibility of their infecting isolate, i.e. PSSA, MSSA & MRSA.
Total index hospitalisation	Initial hospital admission to an acute inpatient facility, including HITH/OPAT/COPAT and stepdown inpatient rehabilitation/post-acute care (if continuous with the initial inpatient admission).

3. STATISTICAL ANALYSIS APPENDIX VERSION INFORMATION

3.1 Core Protocol Overview

The version of the Statistical Appendix is indicated in this document's header and it is designed to support the following overview of the initial platform as outlined in the core protocol.

Silo	Antibiotic Backbone Domain A	Adjunctive Treatment Domain B	Early Oral Switch Domain C
PSSA	(Flu)cloxacillin* Penicillin	No clindamycin* Vs Clindamycin	Usual care* (initial 2-6 week antibiotic backbone treatment course given intravenously) versus early oral switch algorithm (as detailed in the relevant DSA)
MSSA	(Flu)cloxacillin* Cefazolin		
MRSA	Vancomycin* vs Vancomycin plus cefazolin		

Note that domains and interventions may be added or dropped during the life of the platform. This initial design is given only as an illustration of the trial's structure.
*=Comparator/control group

3.2 Core Protocol Version History

The version history of the Core Protocol is documented in the Core Protocol, page 4.

The current version of the Core Protocol is Version 2.0, dated 24 March 2023.

3.3 Domain Specific Appendix Version History

The version history of each of the domain-specific and associated appendices is documented in each appendix. Current versions are listed below:

- Adjunctive Treatment Domain-Specific Appendix, Version 2.0 dated 24 March 2023
- PSSA/MSSA Treatment Domain-Specific Appendix, Version 2.0 dated 24 March 2023
- MRSA Treatment Domain-Specific Appendix, Version 2.0 dated 24 March 2023
- Early Oral Switch Domain-Specific Appendix, Version 2.0 dated 24 March 2023
- PET/CT Domain-Specific Appendix, Version 1.0 dated 24 March 2023
- Paediatric-Specific Appendix, Version 2.0 dated 24 March 2023
- Pregnancy-Specific Appendix, Version 2.0 dated 24 March 2023
- People Who Inject Drugs (PWID)-Specific Appendix, Version 2.0 dated 24 March 2023
- Health Economics Appendix, Version 2.0 dated 24 March 2023
- Microbiology Appendix, Version 2.0 dated 24 March 2023

3.4 Statistical Analysis Appendix Version History

Version 1.0: (Approved by Trial Management Group 30/06/2021) supports the above-named versions of the core protocol (as at section 3.2) and domain specific appendices (as at section 3.3).

Version 2.0: (Approved by Trial Management Group 24/03/2023) supports the latest version of the core protocol (as at section 3.2) and domain specific appendices (as at section 3.3). This version incorporates: (i) two new estimands for the total number of days that an antibiotic is received and the number of days alive and not receiving antibiotics; (ii) updates the statistical models to include adjustments for regions and countries clustered within regions; (iii) provides a statistical model for count endpoints; and (iv) minor grammar or subscript changes to improve clarity.

4. INTRODUCTION

The objective of SNAP is to identify the effect of a range of clinical interventions on all-cause mortality, 90 days after platform entry, in participants with *Staphylococcus aureus* bacteraemia (SAB). The SNAP platform aims to accurately and efficiently collect treatment and outcome data for the purpose of evaluating the comparative effectiveness of alternative treatments. The platform is designed to be adaptive and has the capacity to accommodate additional pharmacological and non-pharmacological interventions either within existing domains or as part of entirely new domains, as both novel treatments and standard of care evolves over time. SNAP is designed with an overarching Bayesian primary model, specified in this Statistical Appendix and further detailed in the statistical implementation guide (SIG), from which posterior distributions driving all adaptations, statistical triggers, and result summaries. This primary statistical analysis model will be used to estimate population level parameters and report trial results.

The focus of this Statistical Appendix is to describe the statistical methods and decision criteria for making trial adaptations, recommending domain- or cell-specific intervention non-inferiority, superiority or futility and reporting final domain analyses. It draws on information in the core protocol and domain specific appendices to define platform and domain objectives, target populations, endpoints, statistical methods and models and population level estimators within the estimand framework (ICH E9 (R1)). It provides a technical bridge between the core protocol and domain specific appendices and the statistical implementation guide (SIG), and is generalisable to the addition of new interventions or domains in the platform. An overview of the methodology for summarising and analysing the accumulating trial data is described, however, more complete details will be provided in the SIG, which will be maintained throughout the lifecycle of the platform by the investigators. The SIG may modify what is outlined in the protocol if appropriate; however, any major modifications of the primary endpoint definition or the primary analysis will be reflected in a protocol amendment.

5. TRIAL STRUCTURE

5.1 Design

SNAP is an investigator initiated, Randomised Embedded Multifactorial Adaptive Platform (REMAP) trial, conducted across multiple hospitals in several regions of the world. Eligible, consented participants will be allocated at random to prescribed interventions, grouped into domains. The platform enables the introduction of new treatments or domains as the trial progresses.

Initial Domains:

- Antibiotic Backbone Domain

- Adjunctive Treatment Domain
- Early Oral Switch Domain
- Other domains may be included at later dates

5.2 Domains and Interventions

A domain defines a set of mutually exclusive, competing treatments sharing a common clinical mode of action or clinical context of use (e.g. primary antibiotics, adjunctive antibiotics). Both the number of domains and the number and identity of individual treatments within each of these domains may vary across the life of the platform as new treatments of interest become available.

Domains are referred to by capitalised alpha-letter for convenience (i.e. A=Backbone antibiotic, B=Adjunctive antibiotic, C=Early oral switch):

$$\boldsymbol{d} = \boldsymbol{A}, \boldsymbol{B}, \ldots, \boldsymbol{Z}$$

Separate intervention products within a particular domain are labelled with the subscript index *k*, where there are $\boldsymbol{d} = \boldsymbol{d_1}, \boldsymbol{d_2}, \ldots, \boldsymbol{d_k}$ interventions within each domain *d*. Under this nomenclature, d_k refers to intervention k within domain d. This labelling will also easily accommodate new interventions or domains should these options expand over time.

5.3 Silos & Subpopulations

A silo is a subgroup of participants who are defined by the antibiotic susceptibility of their infecting isolate, i.e. PSSA, MSSA & MRSA. Domain efficacy will be assessed at the level of the silo (i.e. in a cell), unless stated otherwise in the DSA. The silo is denoted by s and will initially consist of 1=PSSA, 2=MSSA and 3=MRSA, but is flexible to accommodate new (mutually exclusive) silos:

$$\boldsymbol{s} = \mathbf{1}, \mathbf{2}, \ldots, \boldsymbol{S}$$

Adults and paediatric subpopulations are defined as participants aged 18 years or above, and as participants less than 18 years, respectively. Domain efficacy will be assessed separately for adult and paediatric subpopulations at the level of the silo (i.e. in a cell), unless stated otherwise in the DSA. The age subpopulations are denoted by *a* and will consist of 1=Adult and 2=Child, but is flexible to accommodate new (mutually exclusive) age cohorts:

$$\boldsymbol{a} = \mathbf{1}, \mathbf{2}, \ldots, \boldsymbol{A}$$

Statistical models may also include a covariate for age to increase the precision of the estimates (Section 7).

5.4 Randomisation

5.4.1 Description of randomisation

Randomisation of participants to one intervention from each domain for which they are eligible, is performed at platform entry. Participants will be randomised to one intervention from each domain that the site is participating in, according to allocation probabilities detailed in each DSA and stratified by adult and paediatric subpopulations. Since eligibility for the silos and early oral switch domain is unknown at platform entry, it is necessary to generate, but not reveal, individual allocations for each domain until the participant fulfils domain-specific eligibility criteria. Response adaptive randomisation may be applied if a domain has a minimum of at least three active intervention arms at any point during the platform lifecycle.

5.4.2 Response-adaptive randomisation (RAR)

At the commencement of the SNAP platform, the trial will not feature RAR in any of the domains. However, if future domains require RAR then, assignment probabilities for interventions within a domain or cell will initially be equal. Data accumulated on the primary endpoint will subsequently guide allocation probabilities following this run-in period. For each age subpopulation (i.e. adults, paediatrics), randomised assignment probabilities to each domain-specific intervention within a cell or domain, will be permitted to vary across the life cycle of the platform, proportional to the probability that each domain-specific intervention is the most effective in that cell or domain. Allocation probabilities will be based on the results of interim analyses. RAR will be used to update randomisation probabilities as a function of the probability $best(\theta_{a,s,d_k})$ and information weighting for the next group of eligible domain participants as follows:

$$\boldsymbol{q}_{\boldsymbol{a,s,d_k}} \propto \sqrt{\frac{\boldsymbol{prbest}(\boldsymbol{\theta}_{\boldsymbol{a,s,d_k}})\boldsymbol{V}(\boldsymbol{\theta}_{\boldsymbol{a,s,d_k}})}{\boldsymbol{n}_{\boldsymbol{a,s,d_k}}+\boldsymbol{1}}}, \text{ where:}$$

$\boldsymbol{q}_{\boldsymbol{a,s,d_k}}$ = updated randomisation probability for intervention *k* in domain *d* for silo *s* and age subpopulation *a*

$\boldsymbol{prbest}(\boldsymbol{\theta}_{\boldsymbol{a,s,d_k}})$ = the "*probability best*" for intervention *k* in domain *d* for silo *s* and age subpopulation *a*, obtained via the Bayesian posterior distribution for the primary estimand

$\boldsymbol{V}(\boldsymbol{\theta}_{\boldsymbol{a,s,d_k}})$ = estimated variance of the age-, domain- and silo-specific primary estimand

$\boldsymbol{n}_{\boldsymbol{a,s,d_k}}$ = total number of participants with 90 days follow-up who have been allocated to an intervention *k* within a domain *d* for silo *s* and age subpopulation *a*.

5.4.3 Domain-specific and intervention-specific ineligibilities and unavailabilities

Domain-specific ineligibilities are listed in the individual DSAs and may include contraindications (allergies, intolerances, adverse events) and non-contraindication ineligibilities (lack of access, clinician discretion, site opted out of domain). Domain ineligibilities will be managed by including additional indicator variables in the statistical model; where $\boldsymbol{\gamma}_{\boldsymbol{a,s,d}}$ in the primary statistical model is the increment in log odds of the outcome

for participants who are ineligible for domain *d* in silo *s* and subpopulation *a*. If a participant is ineligible for all treatments within a domain and/or an entire treatment domain is unavailable at a site at the time of randomisation, then the participant will also be deemed ineligible for that domain.

If RAR is used, then if a participant is ineligible for one or more interventions within a domain, assignment probabilities will be re-normalised across the remaining eligible interventions, as long as there are a minimum of two eligible interventions within that domain that are available to the participant. If an intervention within a domain is unavailable at randomisation for site-specific reasons (e.g. temporary lack of access to the intervention drug), then assignment probabilities will be re-normalised across the remaining available interventions, as long as there are a minimum of two eligible interventions within that domain that are available to the participant. Data on both the primary and secondary endpoints in participants flagged as ineligible (refused) for some or all interventions will still be captured and available for analysis.

6. ENDPOINTS, ESTIMANDS & INTERCURRENT EVENTS STRATEGY

The trial population of interest is defined on the inclusion and exclusion criteria described in the SNAP core protocol, hereafter known as platform eligible participants. The platform core primary endpoint is the same across all domains and silos for participants aged 18 years or greater.

6.1 Core Protocol Primary Efficacy

Estimand/Objective/ Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 1 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 90 days after platform entry, in platform eligible participants.	Endpoint: All-cause mortality at 90 days after platform entry#. Population summary*: Log odds ratio of mortality between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat principle)

Platform entry is defined as the date that consent was obtained.

* For some domains, the population level summary may be estimated across silos if pre-specified in the DSA.

6.2 Core Protocol Secondary Efficacy & Safety

Estimand / Objective / Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 2 To evaluate, within each relevant cell, the effect of interventions compared to the domain control, on the probability of all-cause mortality at 90 days after platform entry, in platform eligible participants who adhered to treatment.	Endpoint: All-cause mortality at 90 days after platform entry#. Population summary*: As for Estimand 1	Principal stratum strategy (including strata equating to trial compliers and protocol violators)
Estimand 3 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 14 days after platform entry, in platform eligible participants.	Endpoint: All-cause mortality at 14 days after platform entry#. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 4 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 28 days after platform entry, in platform eligible participants.	Endpoint: All-cause mortality at 28 days after platform entry#. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)

Platform entry is defined as the date that consent was obtained.

* For some domains, the population level summary may be estimated across silos, however, this will be pre-specified in the DSA.

Estimand / Objective / Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 5 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of all-cause mortality at 42 days after platform entry, in platform eligible participants.	Endpoint: All-cause mortality at 42 days after platform entry#. Population summary*: As for Estimand 1	Treatment policy strategy (intent-to-treat principle)
Estimand 6 To evaluate, within each relevant cell, 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, in platform eligible participants.	Endpoint: Time to all-cause mortality, censored at 90 days after platform entry#. Population summary*: Log hazard ratio of mortality between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat principle) Any patient currently in the hospital or transferred to an alternative care facility will be censored at their last known status alive. Any patient successfully discharged from hospital, alive, without organ support, will be censored at the date of discharge, if 90-day mortality data are not yet recorded.
Estimand 7 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of total index hospitalisation (time from platform entry to discharged alive for index hospitalisation, including HITH/COPAT/OPAT), truncated at 90 days after platform entry, in platform eligible participants.	Endpoint: Time to discharged alive for total index hospitalisation, including HITH/COPAT/OPAT and truncated at 90 days after platform entry#. Population summary*: Log hazard ratio of discharged alive for index hospitalisation between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat principle) Excludes hospital readmission following total index hospitalisation, even if within 90 days of platform entry. All deaths during the index hospitalisation^ will be considered 90-days with no events. Participants still in the hospital at the time of interim analysis will be considered censored.

Platform entry is defined as the date that consent was obtained.

* For some domains, the population level summary may be estimated across silos, however, this will be pre-specified in the DSA.

^ Total index hospitalisation is defined as a continuous admission to any inpatient healthcare facility, including rehabilitation hospitals, starting from platform entry.

Estimand / Objective / Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 8 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of acute index hospitalisation (time from platform entry to discharge from acute inpatient facilities, excluding HITH/COPAT/OPAT), truncated at 90 days after platform entry, in platform eligible participants who survived until discharge	Endpoint: Time to discharge for acute index hospitalisation^, excluding HITH/COPAT/OPAT and truncated at 90 days after platform entry#. Population summary*: Log hazard ratio of discharge for index hospitalisation between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat principle) Excludes participants who do not survive until hospital discharge and any periods of hospital readmission following index hospitalisation, even if within 90 days of platform entry. Participants still in the hospital at the time of interim analysis will be considered censored.
Estimand 9 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the hazard ratio of duration of the total index hospitalisation (time from platform entry to discharge from index hospitalisation including HITH/COPAT/OPAT) , truncated at 90 days after platform entry, in platform eligible participants who survive until hospital discharge	Endpoint: Time to discharge for the total index hospitalisation^, including HITH/COPAT/OPAT and truncated at 90 days after platform entry#. Population summary*: As for Estimand 8	Treatment policy strategy (intent-to-treat principle) Excludes participants who do not survive until hospital discharge and any periods of hospital readmission following index hospitalisation, even if within 90 days of platform entry. Participants still in the hospital at the time of interim analysis will be considered censored.
Estimand 10 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of microbiological failure between 14 and 90 days after platform entry, in platform eligible participants.	Endpoint: Microbiological treatment failure, defined as positive sterile site culture for *S. aureus* [same silo as the index isolate] between 14 & 90 days after platform entry#. Population summary*: Log odds ratio of microbiological treatment failure between intervention and control groups within a domain (d), estimated for each silo (s) &	Treatment policy strategy (intent-to-treat principle) A sterile site means any sites deep to the skin and skin structures that have been obtained in a sterile manner.

	age subpopulation (a)	

Platform entry is defined as the date that consent was obtained. *For some domains, the population level summary may be estimated across silos, however, this will be pre-specified in the DSA.

^ Total index hospitalisation is defined as a continuous admission to any inpatient healthcare facility, including rehabilitation hospitals, starting from platform entry.

Estimand / Objective / Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 11 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of diagnosis of new metastatic foci between 14 and 90 days after platform entry, in platform eligible participants.	Endpoint: Diagnosis of new metastatic foci between 14 and 90 days after platform entry#. The presence of new metastatic foci will be determined by the site investigator and can incorporate clinical, radiological, microbiological and pathological findings. Population summary*: Log odds ratio of diagnosis of new metastatic foci between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat effect)
Estimand 12 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to domain control, on the probability of diagnosis of *C. difficile* diarrhoea up to 90 days after platform entry, in platform eligible participants ≥2 years of age.	Endpoint: Diagnosis of *C. difficile* diarrhoea as determined by a clinical laboratory in the 90 days following platform entry# for participants ≥2 years of age. This means a stool submitted to a clinical laboratory has tested positive for C. difficile toxin or toxin gene. Population summary*: Log odds ratio of diagnosis of *C. difficile* diarrhoea between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat effect)
Estimand 13 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to domain control, on the probability of serious adverse reactions up to 90 days after platform entry, in platform eligible participants.	Endpoint: Serious adverse reactions (SAR) defined as any SAE that is suspected to be related to a medicinal product used for *S. aureus* bacteraemia in the 90 days following platform entry#. Population summary*: Log odds ratio of SAR between intervention and control groups within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat effect)

Platform entry is defined as the date that consent was obtained.

* For some domains, the population level summary may be estimated across silos, however, this will be pre-specified in the DSA.

Estimand / Objective / Target population	Endpoint / Population level summaries	Intercurrent events strategy
Estimand 14 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to the domain control, on the probability of return to usual level of function (as determined by whether the modified functional bloodstream infection score (FBIS) remained the same or improved) between baseline and 90 days after platform entry, in adult platform eligible participants.	Endpoint: Return to usual level of function 90 days after platform entry #. Population summary*: Log odds ratio of return to normal function between intervention and control groups within a domain (d), estimated for each silo (s) in the adult (18 years or greater) subpopulation.	Treatment policy strategy (intent-to-treat effect)
Estimand 15 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to domain control, on the proportional odds ratio of Desirability Of Outcome Ranking (DOOR1, modified Antibiotic Resistance Leadership Group version) at platform Day 90, in adult platform eligible participants.	Endpoint: DOOR1 score at platform Day 90. Population summary*: Log proportional odds ratio of intervention compared to domain control for being in DOOR1 group j or higher compared to group j-1 or lower, within a domain (d) and estimated for each silo (s) in the adult (18 years or greater) subpopulation.	Treatment policy strategy (intent-to-treat effect)
Estimand 16 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to domain control, on the proportional odds ratio of Desirability Of Outcome Ranking (DOOR2, SNAP version) at platform Day 90, in adult platform eligible participants.	Endpoint: DOOR2 score at platform Day 90. Population summary*: Log proportional odds ratio of intervention compared to domain control for being in DOOR2 group j or higher compared to group j-1 or lower, within a domain (d) and estimated for each silo (s) in the adult (18 years or greater) subpopulation.	Treatment policy strategy (intent-to-treat effect)
Estimand 17 To evaluate, within each	Endpoint: Clinician estimated total number of days on which any antibiotic dose is received	Treatment policy strategy (intent-to-

relevant cell, the effect of revealed randomised interventions compared to domain control, on the clinician estimated number of antibiotic days (IV and/or oral/enteral) in the 90 days following platform entry, in platform eligible participants.	in the 90 days following platform entry. Population summary*: Difference in the log-expected count between the intervention and control group, within a domain (d) and estimated for each silo (s) and age subpopulation (a).	treat effect). Participants who die within 90 days will be recorded as the number of days alive and receiving antibiotic treatment. Participants who are alive but have not reached Day 90 at the time of any interim analyses will be excluded.
Estimand 18 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to 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, in platform eligible participants.	Endpoint: Total number of days alive and free from antibiotics in the 90 days following platform entry#. Participants who die within 90 days will be modelled as having an outcome of –1. Population summary*: Log proportional odds ratio of intervention compared to domain control for having outcome j or higher compared to outcome j-1 or lower, within a domain (d) and estimated for each silo (s) within a domain (d), estimated for each silo (s) and age subpopulation (a).	Treatment policy strategy (intent-to-treat effect)

Platform entry is defined as the date that consent was obtained.

* For some domains, the population level summary may be estimated across silos if pre-specified in the DSA.

6.3 Covariates

The primary statistical model will include age at index hospitalisation. Domain-specific secondary analyses are outlined in the DSAs and further details will be provided in the SIG.

6.4 Intercurrent events

An intercurrent event is one that occurs after the reveal of the allocated intervention(s) and prior to observation of a trial endpoint (primary or secondary). Intercurrent events may include premature discontinuation of the allocated intervention due to intolerance, adverse events or lack of effectiveness, inability to assess an endpoint, treatment switching or the introduction of rescue or symptomatic treatments. Details of intercurrent events likely to be encountered during the conduct of SNAP, including strategies for statistically managing each event, will be detailed in the SIG. However, the general strategies for each objective and estimand are defined in Sections 6.1 and 6.2 above.

7. STATISTICAL MODELLING

7.1 Primary model

A Bayesian hierarchical logistic regression model will be used for the primary analysis. The model estimates the posterior probability of the log odds ratio for each domain intervention (*k*) compared to control by silo or pooled across silos (*s*), for each age subpopulation (*a*). We model the primary endpoint, $\boldsymbol{Y_i} \in \{\mathbf{0}, \mathbf{1}\}$, using a Bernoulli model with a logistic link function such that, $\boldsymbol{Y_i} \sim \boldsymbol{Bernoulli}(\boldsymbol{p_{a,s,d_k}})$ and $\boldsymbol{p_{a,s,d_k}} = \boldsymbol{logit^{-1}}(\boldsymbol{\alpha} + \boldsymbol{\beta_1 X_1} + \cdots + \boldsymbol{\beta_p X_p})$. We assign prior probability distributions to all parameters of the model as described in Section 8.

The primary model accounts for within silo and age subpopulation effects due to interventions within domains ($\boldsymbol{\beta_{a,s,d_k}}$), interactions between treatments from different domains ($\boldsymbol{\varphi_{a,s,d_k,d'_j}}$), ineligibility for a domain ($\boldsymbol{\gamma_{a,s,d}}$), age ($\boldsymbol{\beta_{s,age}}$), region ($\delta_r$) and country ($\omega_{c_r}$). In addition, the model includes parameters corresponding to time, that adjust for temporal trends over the course of the SNAP Platform. The parameters for time are based on time of platform entry and are smoothed across time using a Bayesian second order normal dynamic linear model (NDLM), denoted by $\eta(t)$, unless specified otherwise in the SIG, which will be published on the SNAP website in advance of each interim. The general form of the primary model is given by:

$$\boldsymbol{logit}(\boldsymbol{p_{a,s,d_k}}) = \sum_{\boldsymbol{a=1}}^{\boldsymbol{A}}\sum_{s=1}^{S}\alpha_{a,s} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\beta_{a,s,d_k} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\gamma_{a,s,d} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\sum_{d'=B}^{Z}\sum_{j=1}^{J_{d'}}\varphi_{a,s,d'_j}$$
$$+ \sum_{s=1}^{S}\sum_{age=1}^{9}\beta_{s,age} + \sum_{\boldsymbol{r=1}}^{\boldsymbol{n_R}}\boldsymbol{\delta_r} + \sum_{\boldsymbol{c=1}}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t)$$

At platform commencement the primary model for intervention d_k in silo *s*, within an age subpopulation (i.e. adult or paediatric), is presented below, where:

(i) each domain initially consists of two interventions;

(ii) the effect of adjunctive antibiotic (domain B) is combined over all silos;

(iii) domain-domain interventions are restricted to the MRSA silo (s=3) for backbone and adjunctive antibiotic domains (d=A and d'=B).

$$\boldsymbol{logit}(p_{a,s,d_k}) = \boldsymbol{\alpha_{a,s}} + \boldsymbol{\beta_{a,s,A_k}} + \boldsymbol{\beta_{a,B_k}} + \boldsymbol{\beta_{a,s,C_k}} + \boldsymbol{\gamma_{a,s,A}} + \boldsymbol{\gamma_{a,s,B}} + \boldsymbol{\gamma_{a,s,C}} + \boldsymbol{\varphi_{a,s=3,A_k,B_j}}$$
$$+ \sum_{\boldsymbol{age=1}}^{\boldsymbol{9}}\boldsymbol{\beta_{s,age}} + \sum_{\boldsymbol{r=1}}^{\boldsymbol{8}}\boldsymbol{\delta_r} + \sum_{\boldsymbol{c=1}}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t)$$

The effect estimators can be interpreted as:

$\boldsymbol{p_{a,s,d_k}}$ = probability of mortality 90 days after platform entry for age subpopulation *a*, in silo *s*, adjusting for domain interventions, eligibility for domain *d*, interactions across domain interventions and age;

$\boldsymbol{\alpha_{a,s}}$= log-odds of mortality for age subpopulation *a*, in silo *s* for eligible domain controls and reference age group;

$\boldsymbol{\beta_{a,s,A_k}}$= log odds ratio of mortality for age subpopulation *a*, in Domain *A*, intervention *k* compared to control for silo s, adjusted for domain eligibilities;

$\boldsymbol{\beta_{a,B_k}}$= log odds ratio of mortality for age subpopulation *a*, in Domain *B,* intervention *k* compared to control, pooled over silos, adjusted for domain eligibilities;

$\boldsymbol{\beta_{a,s,C_k}}$= log odds ratio of mortality for age subpopulation *a*, in Domain *C,* intervention *k* compared to control, for silo *s*, adjusted for domain eligibilities;

$\boldsymbol{\gamma_{a,s,A}}$= log odds ratio of mortality for age subpopulation *a*, for ineligible compared to eligible for Domain *A* in silo *s;*

$\boldsymbol{\gamma_{a,s,B}}$= log odds ratio of mortality for age subpopulation *a*, for ineligible compared to eligible for Domain *B* in silo *s;*

$\boldsymbol{\gamma_{a,s,C}}$= log odds ratio of mortality for age subpopulation *a*, for ineligible compared to eligible for Domain *C* in silo *s;*

$\boldsymbol{\varphi_{a,s=3,A_k,B_j}}$= log odds ratio of mortality for the interaction between Domain *A* intervention *k* and Domain *B* intervention *j* in the MRSA silo for subpopulation *a;*

$\boldsymbol{\beta_{s,age}}$= log odds ratio of mortality for age group '*age*' relative to reference age group for silo s, where $\boldsymbol{age} \in \{\mathbf{1}, \mathbf{2}, \mathbf{3}, \mathbf{4}, \mathbf{5}, \mathbf{6}, \mathbf{7}, \mathbf{8}, \mathbf{9}\}$ and 1="<30 days", 2="31-365 days", 3="366 days–4 years", 4="5–11 years", 5="12–17 years", 6="18—39 years", 7="40–59 years", 8="60–79 years", and 9="80 years and over".

δ_r=log odds ratio of region where $r \in \{1,2,3,4,5,6,7,8\}$, and 1 ="Africa and the Middle East (excluding Israel)", 2="East Asia", 3="Europe (including Israel)",4="Oceania", 5="North America", 6="South and Central America", 7="South-east Asia", 8="Subcontinental Asia"}.

ω_{c_r}= log odds ratio of country (nested within region).

$\eta(t)$= temporal trends smoothed across time using a Bayesian second order NDLM

Decision criteria for trial adaptations or domain conclusions will be based on quantities of interest (odds ratios) for the adult model parameters, incorporating the evidence for each intervention that has been gathered through the course of the trial from adult and paediatric participants and the model prior distributions (assumed prior knowledge, see Section 8), unless superseded by DSA-specific priors. The primary analysis will be conducted on an Intention-To-Treat (ITT) principle; participants will be compared based on the interventions revealed, accounting for domain ineligibilities. For the primary analysis, the model will estimate separately for each age subpopulation (adult and paediatric), the log odds ratios for each intervention compared to control within a domain for each silo (aka cell). Stopping decisions in each cell are based on adult model parameters and determine whether the posterior probabilities that the intervention is **non-inferior** or **superior,** with respect to the relevant domain control, are above, or below, pre-specified thresholds, unless superseded by DSA-specific decision criteria. Where a cell stopping decision is recommended because a posterior probability is below the pre-specified threshold, we say that it is futile to continue with the objective of demonstrating non-inferiority or superiority, whichever is relevant. Full details are provided in Section 10.

7.2 Sensitivity analyses of the primary model

Inferences for an estimand need to be robust to the limitations in the data and deviations from the assumptions used in the statistical model. Sensitivity analyses are planned for the core protocol primary estimand to investigate the effect of the choice of Bayesian hierarchical model priors on the population level parameter estimate, i.e. log odds ratios for each intervention compared to control for each cell and subpopulation. Priors will be explored that promote or inhibit information sharing (borrowing) across silos and detailed in the SIG.

The effect of treatment adherence on the primary endpoint will be quantified in Estimand 2 (comparable to a per protocol analysis). Estimand 2 is a secondary analysis and will exclude participants for early treatment

discontinuation, treatment switching or other modifications to the randomised intervention that involve the study participant not receiving the full course of their allocated treatment between revealed allocation and assessment of the primary endpoint 90 days after platform entry.

7.3 Secondary models

7.3.1 Binary endpoints

A similar Bayesian hierarchical model, outlined in Section 7.1, will be used to model all secondary binary endpoints.

7.3.2 Time to event endpoints

A Bayesian Weibull proportional hazards model (or accelerated failure model) will be used for time to event endpoints. The model estimates the posterior probability of the log hazard for each domain intervention (*k*) compared to control by silo (or pooled across silos) and age subpopulations. We model time to event endpoints, $\boldsymbol{T_{a,s,d_k}} \in \{\mathbb{R}_{\geq 0}\}$, using proportional hazards such that, $\boldsymbol{T_{a,s,d_k}} \sim \boldsymbol{W(\lambda_{a,s,d_k}, \kappa)}$, $\boldsymbol{\lambda_{a,s,d_k}} = \boldsymbol{exp}\left(\boldsymbol{\alpha} + \boldsymbol{\beta_1 X_1} + \cdots + \boldsymbol{\beta_p X_p}\right)$ and $\boldsymbol{h(T_{a,s,d_k})} = \boldsymbol{\lambda_{a,s,d_k} \kappa t^{\kappa-1}}$. We assign an exponential prior probability distribution to the shape parameter $\boldsymbol{\kappa}$ and normal prior probability distributions to the linear predictors $\boldsymbol{\alpha}, \boldsymbol{\beta}$ (described in Section 8). The general form of the model for time-to-event endpoints is given by:

$$\boldsymbol{h(T_{a,s,d_k})} = \boldsymbol{\lambda_{a,s,d_k} \kappa t^{\kappa-1}}, \text{ where}$$

$$\boldsymbol{\lambda_{a,s,d_k}} = \boldsymbol{exp}\,(\sum_{a=1}^{A}\sum_{s=1}^{S}\alpha_{a,s} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\beta_{a,s,d_k} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\gamma_{a,s,d} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\sum_{d'=B}^{Z}\sum_{j=1}^{J_{d'}}\varphi_{a,s,d_k,d'_j} + \sum_{s=1}^{S}\sum_{age=1}^{9}\beta_{s,age} + \sum_{r=1}^{\boldsymbol{n_R}}\boldsymbol{\delta_r} + \sum_{c=1}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t)$$

The effect estimators can be interpreted as follows (further details will be available in the SIG):

$\boldsymbol{T_{a,s,d_k}}$ describes the Weibull probability density with scale parameter $\boldsymbol{\lambda_{a,s,d_k}}$ and shape parameter $\boldsymbol{\kappa}$ in silo *s* for intervention *k* within domain *d* for age subpopulation *a*;
$\boldsymbol{h(T_{a,s,d_k})}$ or the hazard function (aka instantaneous failure rate or force of mortality) is an estimator of the rate of death at an instant *t*, given survival up to time *t*, in silo s for intervention *k* within domain *d* for age subpopulation *a*;
$\boldsymbol{\lambda_{a,s,d_k}}$ is the scale parameter of the Weibull distribution in silo *s* for intervention *k* within domain d for age subpopulation *a*, and is estimated using a linear predictor similar in hierarchical structure to the primary statistical model;

$\boldsymbol{\kappa}$ is the shape parameter of the Weibull distribution and is assumed to be fixed; $\kappa > 1$ implies increasing hazard, $\kappa < 1$ a deceasing hazard and $\kappa = 1$ is a constant hazard.
Remaining components of the linear model are parameterised as in the Primary model.

7.3.3 Ordinal (ordered categorical) endpoints

A proportional odds model will be used for ordinal endpoints. This includes core protocol estimands 15-16. The model estimates the posterior distribution of the proportional odds ratio between each domain intervention (*k*) and the domain control, by silo or pooled across silos, for each age subpopulation. We model the ordinal endpoint $Y_i = m$, where $m \in \{1,2,\dots,M\}$ indicates membership of ordered group *m*, using a multinomial model with a cumulative logit link (aka proportional odds model).

$$Y_i \sim Multinomial(1, \boldsymbol{\pi})$$

$$\eta_{a,s,d_k,j} = logit^{-1}(\sum_{a=1}^{A}\sum_{s=1}^{S}\alpha_{a,s} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\beta_{a,s,d_k} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\gamma_{a,s,d} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\sum_{d'=B}^{Z}\sum_{j=1}^{J_{d'}}\varphi_{a,s,d_k,d'_j}$$
$$+ \sum_{s=1}^{S}\sum_{age=1}^{9}\beta_{s,age} + \sum_{\boldsymbol{r=1}}^{\boldsymbol{n_R}}\boldsymbol{\delta_r} + \sum_{\boldsymbol{c=1}}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t))$$

where $\boldsymbol{\pi} = \{\pi_1, \pi_2, \dots, \pi_{M-1}\}$ is the vector of probabilities with each element being the probability of belonging to group m, and $logit(\eta_{a,s,d_k,m}) = \log\left(\frac{P(Y_{a,s,d_k} \leq m)}{P(Y_{a,s,d_k} > m)}\right)$.

At platform commencement, the effect estimators can be interpreted as follows for group j:

$\boldsymbol{\alpha_{a,s}}$= log-odds of response being in group m or higher compared to group *m-1* or lower, in silo *s* for domain controls and age subpopulation *a*,

$\boldsymbol{\beta_{a,s,A_k}}$= additive effect of interventions in domain *A* on the log odds of being in group *m* or higher compared to group *m-1* or lower, on domain control for silo *s* and age subpopulation *a*,

$\boldsymbol{\beta_{a,B_k}}$= additive effect of interventions in domain *B* on the log odds of being in group *m* or higher compared to group *m-1* or lower, on domain control, pooled over silos in age subpopulation a,

$\boldsymbol{\beta_{a,s,C_k}}$= additive effect of interventions in domain *C* on the log odds of being in group *m* or higher compared to group *m-1* or lower, on domain control for silo s and age subpopulation a,

Remaining components of the linear model are parameterised as in the Primary model.

7.3.4 Continuous endpoints

A Bayesian hierarchical linear model will be used for continuous endpoints including in the DSAs. The model estimates the posterior distribution of the mean difference between each domain intervention (*k*) and the domain control, by silo (or pooled across silos) and age subpopulation. We model continuous endpoints, $\boldsymbol{Y_i} \in \{\mathbb{R}\}$, using a general linear model with normally distributed residuals such that, $\boldsymbol{Y_i} \sim \boldsymbol{N}(\boldsymbol{\mu_{a,s,d_k}}, \boldsymbol{\sigma^2})$, and

$\boldsymbol{\mu_{a,s,d_k}} = \left(\boldsymbol{\alpha} + \boldsymbol{\beta_1 X_1} + \cdots + \boldsymbol{\beta_p X_p}\right)$. We assign normal prior probability distributions to all parameters of the model (described in Section 8).

The general form of the model is given by:

$$\boldsymbol{\mu_{a,s,d_k}} = \sum_{a=1}^{A}\sum_{s=1}^{S}\alpha_{a,s} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{k_d}\beta_{a,s,d_k} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\gamma_{a,s,d} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\sum_{d'=B}^{Z}\sum_{j=1}^{J_{d'}}\varphi_{a,s,d_k,d'_j}$$
$$+ \sum_{s=1}^{S}\sum_{age=1}^{9}\beta_{s,age} + \sum_{\boldsymbol{r=1}}^{\boldsymbol{n_R}}\boldsymbol{\delta_r} + \sum_{\boldsymbol{c=1}}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t)$$

These effect estimators are interpreted as:

$\boldsymbol{\mu_{a,s,d_k}}$ is the expected value of the endpoint in silo *s* and age subpopulation *a*, accounting for interventions *k* within domains *d*, eligibility for domains *d*, interactions between domain interventions and age;

Remaining components of the linear model are parameterised as in the Primary model.

7.3.5 Count endpoints

A Poisson model will be used for count data. We model the integer number of events for each participant using the Poisson distribution, $Y_i \sim Poisson(\phi_i)$, with a log link function. The model estimates the posterior distribution of the expected number of events for each domain intervention (*k*), by silo or pooled across silos, for each age subpopulation.

$$\log\left(\phi_{a,s,d_k}\right) = \sum_{a=1}^{A}\sum_{s=1}^{S}\alpha_{a,s} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{k_d}\beta_{a,s,d_k} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\gamma_{a,s,d} + \sum_{a=1}^{A}\sum_{s=1}^{S}\sum_{d=A}^{Z}\sum_{k=1}^{K_d}\sum_{d'=B}^{Z}\sum_{j=1}^{J_{d'}}\varphi_{a,s,d_k,d'_j}$$
$$+ \sum_{s=1}^{S}\sum_{age=1}^{9}\beta_{s,age} + \sum_{\boldsymbol{r=1}}^{\boldsymbol{n_R}}\boldsymbol{\delta_r} + \sum_{\boldsymbol{c=1}}^{\mathbf{n_{c_r}}}\boldsymbol{\omega_{c_r}} + \eta(t)$$

Where:

ϕ_{a,s,d_k}=the expected number of the countable event (e.g. days) for age subpopulation a, in silo s, and for intervention d_k.

Remaining components of the linear model are parameterised as in the Primary model.

7.4 Sensitivity analyses in secondary models

Sensitivity analyses and secondary models will be outlined in each DSA and detailed in the SIG.

7.5 Missing data

Participants without primary endpoint data will be excluded from the analysis, although it is anticipated that this will be a rare occurrence. Missing endpoint data will not be imputed for the primary analysis. Covariate data may be imputed and methods will be detailed in the SIG.

8. MODEL PRIOR DISTRIBUTIONS

8.1 Silo Effects

Each silo, for each age subpopulation, will have a baseline effect for the adult subpopulation, denoted by α_s, where $s = 1,2,\dots,S$. For all silos, the α_s, are given priors:

$$[\alpha_{a,s}] \sim N(-2, 10^2)$$

8.2 Intervention Common Effects

Each intervention parameter β_{a,s,d_k}, for age subpopulation $a = 1,2,\dots,A$, silo $s = 1,2,\dots,S$ and domain intervention $d_k = d_1, d_2, \dots, d_{k_d}$ (where K_d is the total number of interventions in domain *d*), is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain (d_1) is set to 0 in both adult and paediatric subpopulations. Each domain-specific appendix will specify whether intervention effects should be modeled independently (non-nested) for each silo, pooled across the silos or using information sharing (borrowing) across the silos.

For all non-nested interventions, the silo-specific intervention effects are modeled separately in each silo, with hierarchical borrowing across age subpopulations:

$$[\beta_{a,s,d_k}] \sim N(\mu_{s,d_k}, \tau^2_{s,d_k})$$

with hyperpriors:

$$[\mu_{s,d_k}] \sim N(0, 1^2)$$
$$[\tau^2_{s,d_k}] \sim IG(1, 0.0625)$$

The prior on the variance term places the expected standard deviation around 0.25 with a weight of 2.

For some domains, there may be interventions that have an anticipated similar effect across all silos. For these domains, the intervention effects are modeled hierarchically, which allows information sharing (borrowing) across the silos for an age subpopulation. For domain interventions where information sharing across silos is pre-specified, the hyperparameters are selected such that the prior for $\tau_{\beta_{a,d_k}}$ is centered at 0.1. The prior is:

$$[\beta_{a,s,d_k}] \sim N(\mu_{\beta_{a,d_k}}, \tau^2_{\beta_{a,d_k}})$$

with the prior variance modelled as:

$$\left[\tau^2_{\beta_{a,d_k}}\right] \sim IG(0.1, 0.0025)$$

The mean value has a hierarchical structure that borrows across age subpopulations:

$$[\mu_{\beta_{a,d_k}}] \sim N\left(\mu_{\beta_{d_k}}, \tau^2_{\beta_{d_k}}\right)$$
$$[\mu_{\beta_{d_k}}] \sim N(0, 1^2)$$
$$\left[\tau^2_{\beta_{d_k}}\right] \sim IG(1, 0.0625)$$

For domain interventions where modeling using pooling across silos is pre-specified, we estimate the pooled effect within each age subpopulation, and borrow across age subpopulations:

$$[\beta_{a,d_k}] \sim N(\mu_{\beta_{d_k}}, \tau^2_{\beta_{d_k}})$$
$$[\mu_{\beta_{d_k}}] \sim N(0, 1^2)$$
$$\left[\tau^2_{\beta_{d_k}}\right] \sim IG(1, 0.0625)$$

8.3 Domain Eligibility Effects

Where a participant is ineligible for a domain (for example, due to contraindication) an indicator variable will be created for each combination of domain and age subpopulation, and included in the primary and secondary models. The coefficients for these ineligibility indicators will have the following priors:

$$[\gamma_{a,s,d}] \sim N(0,1)$$

8.4 Intervention by Intervention Interaction Effects

It is anticipated that there may be interactions between some interventions in different domains, but that these would likely be relatively small. All two-way interaction parameters will be identified in the DSAs. For all two-way interaction parameters, we define two choices for modeling purposes. One of the following options will be pre-specified for each intervention-intervention pair:

- The model may force no interaction between a pair of interventions by setting the interaction parameter equal to zero. That is, $\boldsymbol{\varphi}_{\boldsymbol{a,s,d_k},d'_j} = 0$ for the interaction between intervention *k* in domain *d* and intervention *j* in domain *d'* (where $d \neq d'$) for silo *s* and age subpopulation *a*.
- In contrast, where an interaction is biologically plausible, the interaction term may be given a weak prior:

$$[\boldsymbol{\varphi}_{\boldsymbol{a,s,d_k},d'_j}] \sim N(0, 1^2)$$

8.5 Age Effects

Age effects will be modelled for participants; $age \in \{1, 2, 3, 4, 5, 6, 7, 8, 9\}$, where 1="<30 days", 2="31-365 days", 3="366 days–4 years", 4="5–11 years", 5="12–17 years", 6="18—39 years", 7="40–59 years", 8="60–

79 years", and 9="80 years and over". For identifiability, the age parameter for the age group 40 to 59 years, will be set to 0. We model the remaining age effects with weakly informative independent normal priors, although more informative priors may be considered in the statistical implementation guide due to anticipated small recruitment sizes in the lower age groups:

$$\left[\beta_{s,age}\right] \sim N(0, 10^2)\,; age = 1,2,3,5,6,7,8,9$$

Where there are fewer than 5 observations in a bin, the Analytic Team may choose to merge that bin with a neighbouring bin at their discretion.

8.6 Regions and countries

Region and country effects will be modelled for participants with country nested within region. The effect of region $r \in \{1, \dots, n_R\}$ is captured using the following parameter:

$$[\delta_r] \sim N(0,1^2).$$

Within region, the effect of country $c_r \in \{1, \dots, n_{c_R}\}$ is captured by the parameter:

$$\left[\omega_{c_r}\right] \sim N(0, \tau^2), [\tau^2] \sim \text{InvGamma}(1, 1/16).$$

8.7 Time Effects

Sensitivity analyses for the primary estimand will include time effects. Time epochs of 26 weeks will be measured from the commencement of the trial. The most recent time period or epoch is denoted $\boldsymbol{\theta_T}$ and will be set to baseline (i.e. zero). For all pre-$\boldsymbol{\theta_T}$ epochs, the prior parameter distributions will be modelled using a first-order normal dynamic "walk-back" linear model (NDLM) as follows:

$$[\theta_{T-1}] \sim N(\theta_T, \tau_T^2); \quad T = 1, \dots, N_T - 1,$$

The initial estimate of the hyper-prior on the drift parameter is given below, however, this may be amended in the SIG:

$$[\tau_T^2] \sim IG(0.25,0.1).$$

The NDLM model for the eras allows borrowing (smoothing) the estimate of each era over the course of the trial. The drift parameter τ_T^2 is the variance component that creates the amount of borrowing from one era to the next. This is shaped by the data, using a hyper-prior distribution. The prior distribution is equivalent to 1 observation worth of data that the era effects have small changes, 0.10^2, from one era to the next. The individual era effects will be heavily shaped by the data from participants within the eras.

9. STATISTICAL QUANTITIES

9.1 Quantities of Interest

The domain intervention quantities of interest (odd ratios) will be derived from the primary estimand (section 6.1) using the primary model (section 7.1). Model parameter posterior probability densities will be employed to inform trial adaptation decisions and to report to the DSMC, in addition to quantifying intervention effects in any trial publications. Early stopping rules will be based on the quantities of interest for the adult model parameters, although these posterior distributions are informed by the paediatric data due to Bayesian information sharing. Decision thresholds will not be defined for the paediatric subpopulation, unless at the request of the DSMC due to safety or efficacy concerns (further details in Section 6 of the Paediatric-Specific Appendix). Quantities of interest for both age subpopulations will be reported to the DSMC in the unblinded efficacy reports.

The following posterior probabilities for the adult subpopulation ($\boldsymbol{a} \in \{\mathbf{1} = \text{Adults, 18 years or greater}\}$) will be reported for the initial platform design:

Quantities of Interest (text)	**Quantities of Interest**	**Threshold**
Domain $\boldsymbol{d} \in \{\boldsymbol{A} = \boldsymbol{Backbone\ antibiotic}\}$, silos $\boldsymbol{s} \in \{\mathbf{1} = \boldsymbol{PSSA}, \mathbf{2} = \boldsymbol{MSSA}\}$, intervention k non-inferior to control: ie. penicillin non-inferior to flucloxacillin for silo PSSA, cefazolin non-inferior to flucloxacillin for silo MSSA.	pr(exp $(\boldsymbol{\beta}_{1,1,A_k}) < 1.2$) pr(exp $(\boldsymbol{\beta}_{1,2,A_k}) < 1.2$)	0.99
Domain $\boldsymbol{d} \in \{\boldsymbol{A} = \boldsymbol{backbone\ antibiotic}\}$, silo $\boldsymbol{s} \in \{\mathbf{1} = \boldsymbol{PSSA}, \mathbf{2} = \boldsymbol{MSSA}\}$, intervention k superior to control: i.e. penicillin superior to flucloxacillin for silo PSSA, cefazolin superior to flucloxacillin for silo MSSA.	pr(exp $(\boldsymbol{\beta}_{1,1,A_k}) < 1$) pr(exp $(\boldsymbol{\beta}_{1,2,A_k}) < 1$)	0.99
Domain $\boldsymbol{d} \in \{\boldsymbol{A} = \boldsymbol{backbone\ antibiotic}\}$, silo $\boldsymbol{s} \in \{\boldsymbol{C} = \boldsymbol{MRSA}\}$, intervention k superior to control: i.e. vancomycin+cefazolin superior to vancomycin alone for silo MRSA.	pr(exp $(\boldsymbol{\beta}_{1,3,A_k}) < 1$)	0.99
Domain $\boldsymbol{d} \in \{\boldsymbol{B} = \boldsymbol{adjunctive\ antibiotic}\}$, intervention k superior to control: i.e. clindamycin superior to no-clindamycin.	pr(exp $(\boldsymbol{\beta}_{1,,B_k}) < 1$)	0.99

Domain $\boldsymbol{d} \in \{\boldsymbol{C} = \boldsymbol{early\ oral\ switch}\}$, silo $\boldsymbol{s} \in \{\mathbf{1}, \mathbf{2}, \ldots \boldsymbol{S}\}$, intervention k non-inferior to control: i.e. early oral switch non-inferior to continued IV in each silo.	pr(exp $(\boldsymbol{\beta}_{1,1,C_k}) < 1.2$) pr(exp $(\boldsymbol{\beta}_{1,2,C_k}) < 1.2$) pr(exp $(\boldsymbol{\beta}_{1,3,C_k}) < 1.2$)	0.99

9.2 Non-inferiority

Non-inferiority of any investigational drug versus the standard of care is defined for the adult subpopulation as an intervention odds ratio (exp($\boldsymbol{\beta}_{\boldsymbol{a}=\mathbf{1},\boldsymbol{s},\boldsymbol{d}_k}$)) of less than 1.2 for the primary endpoint (where OR > 1 indicates an increase in mortality). The clinical minimally important difference is defined to be an upper limit for the odds ratio of 1.2, corresponding to an absolute difference of 3% if the mortality rate in the control arm is 0.15.

$$\boldsymbol{Pr}\left(\boldsymbol{exp}(\boldsymbol{\beta}_{\boldsymbol{a}=\mathbf{1},\boldsymbol{s},\boldsymbol{d}_k}) < \mathbf{1.2}\right) > \mathbf{0.99}$$

Within each cell, if non-inferiority is demonstrated at a pre-specified interim analysis, which is defined as the posterior probability of non-inferiority in that cell of greater than 99%, recruitment into the cell may continue to seek a conclusion of superiority or stop, based on pre-specified decision rules in the DSA.

9.3 Superiority

Superiority of any investigational drug versus the standard of care is defined for the adult subpopulation as an intervention odds ratio (exp($\boldsymbol{\beta}_{\boldsymbol{a}=\mathbf{1},\boldsymbol{s},\boldsymbol{d}_k}$)) of less than 1.0 for the primary endpoint (where OR > 1 indicates an increase in mortality). Within each cell, a stopping decision for superiority will be made if, at a pre-specified interim analysis, the posterior probability of superiority in that cell is greater than 99% and recruitment into the cell may stop, based on pre-specified decision rules in the DSA.

$$\boldsymbol{Pr}\left(\boldsymbol{exp}(\boldsymbol{\beta}_{\boldsymbol{a}=\mathbf{1},\boldsymbol{s},\boldsymbol{d}_k}) < \mathbf{1}\right) > \mathbf{0.99}$$

9.4 Futility for Non-inferiority

A cell stopping decision will be made for futility of the non-inferiority objective if, at a pre-specified interim analysis in the adult subpopulation, the posterior probability of non-inferiority in that cell is less than 1% and recruitment into the cell may stop, based on pre-specified decision rules in the DSA.

$$\boldsymbol{Pr}\left(\boldsymbol{exp}(\boldsymbol{\beta}_{\boldsymbol{a}=\mathbf{1},\boldsymbol{s},\boldsymbol{d}_k}) < \mathbf{1.2}\right) < \mathbf{0.01}$$

9.5 Futility for Superiority

A cell stopping decision for futility of the superiority objective will be made if, at a pre-specified interim analysis in the adult subpopulation, the posterior probability of an intervention odds ratio (exp($\boldsymbol{\beta}_{a=1,s,d_k}$)) of less than 0.83 (i.e. 1/1.2=0.83) for the primary endpoint in that cell is less than 1% and recruitment into the cell may stop, based on pre-specified decision rules in the DSA.

$$\boldsymbol{Pr\left(exp(\beta_{a=1,s,d_k}) < 0.83\right) < \ 0.01}$$

10. BAYESIAN UPDATES (INTERIMS) AND TRIAL ADAPTATIONS

The trial design is an adaptive perpetual platform design that simultaneously evaluates multiple interventions grouped by comparable modes of action or contexts of care (domains). It is designed to be perpetual and answer clinician and consumer priority-driven research questions for *Staphylococcus aureus* bacteraemia (SAB). The trial will involve regular Bayesian updates, efficiently assessing pre-planned decision criteria based on the accruing body of evidence, to answer research questions and minimise the time until public disclosure of results. The pre-planned adaptations include stopping recruitment into a domain or cell for superiority, non-inferiority or futility (see Sections 9.2-9.5), and adding new interventions in an existing domain or adding new domains, subject to available resources. Similarly, interventions may be removed based on trial results or other prevailing conditions, under the guidance of the DSMC and GTSC. There will be a platform starting status with regard to age subpopulations, silos, domains, and the interventions within a domain (see Section 3.1). The Bayesian hierarchical models that derive the posterior probability distributions for model parameters and the decision criteria based on these posterior probability distributions, have been designed to accommodate these trial adaptations.

10.1 Data Sources

All eligible participants in the platform trial will become a part of the accruing trial data and comprise the analysis population for the primary estimand (Section 6.1). All participants defined for the analysis of the primary estimand will remain in that population for as long as the trial is running. Blinded data will be extracted from the SNAP trial database immediately prior to each Bayesian update and provided to the SNAP Analytic Team.

10.2 Estimand for trial adaptations

Estimand 1 (Section 6.1) for the adult subpopulation will be used for all trial adaptations, unless specified otherwise in the DSA.

10.3 Model for trial adaptations

The primary statistical model (Section 7.1) will be used to estimate posterior probability distributions for model parameters for all decision criteria that may result in trial adaptations, unless specified otherwise in the DSA.

10.4 Frequency and timing of Bayesian updates (interims)

The first platform Bayesian update (interim) will be performed after 500 eligible platform participants (adults and paediatrics combined) have completed 90 days of follow-up ("completers"); thereafter, updates will be performed, perpetually, every 500 additional completers for the remainder of the trial. Only data for eligible participants reaching platform Day 90 will be used in the primary analysis to avoid biases that may arise from differential timing of known death compared with known survival. At each update, the primary model (Section 7.1) will be used to assess decision criteria, determining superiority, non-inferiority, and futility, and may inform the next block of allocation ratios if RAR is employed. These decision rules are presented in Section 9.2-9.5.

10.5 Introduction of New Interventions in a Domain

If a new intervention is added while a domain or cell is still active (i.e. allocations are still being made to at least two interventions in the domain or cell), then the randomisation will be "blocked" for the new intervention in order to guarantee an initial sample size. If there are k_d interventions in a domain with the introduction of the new intervention, a fixed allocation of $1/k_d$ will be used to allocate participants to the new intervention. The remaining $1 - (\frac{1}{k_d})$ probability will be allocated to the other interventions either equally or with probability determined RAR, depending on the DSA. This initial phase for each new intervention will last until the next Bayesian update. At that point this restriction will be removed and adaptive randomisation to all regimens may be performed if specified in the DSA, otherwise equal allocations will be performed to all domain interventions.

10.6 Intervention Efficacy Announcement (inc. non-inferiority or superiority)

At each Bayesian update (interim), performed by the SNAP Analytic Team, the results can trigger adaptive decision rules for efficacy, including for non-inferiority or superiority (see Section 9.2-9.3), and may indicate a Public Disclosure of the results and/or removal of interventions within cells or domains. In either case, the Analytic Team will prepare an unblinded report for the DSMC who will make recommendations to the GTSC.

Within each cell or domain, if non-inferiority is demonstrated at a pre-specified interim, recruitment into the cell may continue to seek a conclusion of superiority, based on pre-specified rules in the DSA and recommendations from the DSMC and TSC. There is no automatic adaptation when the threshold for non-inferiority is met. Within each cell, if superiority is demonstrated at a pre-specified interim, the remaining interventions in the domain will be halted for inferiority for that cell. All future participants in that cell may then be deterministically allocated to the superior intervention or treatment may be left to treating clinician choice, with the choice of treatment recorded in the trial database. This will continue unless/until new interventions are added to the domain that contains the superior intervention.

10.7 Intervention Futility

At each Bayesian update (interim), performed by the SNAP Analytic Team, the results can trigger adaptive decision rules for futility, including futility for non-inferiority or futility for superiority (see Section 9.4-9.5), and may indicate a Public Disclosure of the results and/or removal of interventions within cells or domains. In either case, the Analytic Team will prepare an unblinded report for the DSMC who will make recommendations to the GTSC on whether a domain conclusion has been reached and whether to trigger a Public Disclosure. If so, no additional participants in that cell will be randomised to that intervention. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions the rules are always met simultaneously), then the result may be released identifying the superior intervention or may be delayed until the results for all cells within a domain are known.

10.8 Prespecified actions for if a platform conclusion is reached in the MSSA backbone cell prior to in the PSSA backbone cell

Here we pre-specify a simultaneous discontinuation of an existing intervention and addition of a new intervention (replacement) to the PSSA silo backbone antibiotic domain cell in the event of cell conclusions in the MSSA silo backbone antibiotic domain cell. This is due to the inclusion of a (flu)cloxacillin arm in those two cells. A declaration of non-inferiority or superiority of (flu)cloxacillin compared to cefazolin in the MSSA silo backbone antibiotic domain cell may have an impact on clinician willingness to enrol and randomise participants to the PSSA silo backbone antibiotic domain cell. The following pre-specified adaptations have been informed by a clinician survey conducted prior to study initiation.

- At an interim analysis, if cefazolin is found to be non-inferior to (flu)cloxacillin (Domain A) in the MSSA cell and futility is met (i.e., it is futile to continue randomising participants to detect superiority), a conclusion will be declared for the MSSA cell (as per section 9.5), and within the Domain A PSSA cell there will be no change (i.e., continue to assess penicillin versus (flu)cloxacillin).

- At an interim analysis, if cefazolin is found to be superior to (flu)cloxacillin (Domain A) in the MSSA cell, a conclusion will be declared for the MSSA cell (as per section 9.3), and within the Domain A PSSA cell the (flu)cloxacillin arm will be discontinued. The results of the Domain A PSSA cell comparison between penicillin and (flu)cloxacillin will also be declared at this time. If in the PSSA cell, penicillin is inferior to (flu)cloxacillin (as per section 9.5), then we would cease randomisation in this cell and recommend all patients be treated with cefazolin. If in the PSSA cell, penicillin is either superior or non-inferior to (flu)cloxacillin (as per sections 9.2-9.3), or no decision criteria have been met (i.e. insufficient accrual), then cefazolin will be added as a new intervention to the Domain A PSSA cell (i.e in effect, we replace (flu)cloxacillin with cefazolin as the comparator).

10.9 Deviation from Pre-specified Analyses

The SNAP Analytic Team will monitor the primary and secondary model behaviour, including numerical stability and scientific appropriateness. Simpler models may need to be constructed and evaluated determining any root cause issues, data issues, or inappropriate model fit. If any numeric instabilities can be fixed using alternative appropriate statistical methods, these will be performed by the Analytic Team and the adjustments recorded and communicated to the DSMC. If the model is deemed to provide an inappropriate fit then the Analytic Team will inform the DSMB of appropriate adjustments, which will be reported to the GTSC in a way that does not risk unblinding trial results.

11. TRIAL SIMULATIONS

The goal of these simulations is to understand the operating characteristics of the SNAP platform trial and use these to select: (i) the number and timing of interim analyses; and (ii) decision thresholds that maintain a type 1 error of ≤7% (for superiority and non-inferiority) and power >80%. This report is based on the status of the trial simulations on June 30, 2021. Further details will be provided in the Statistical Implementation Guide and, if appropriate, may be documented in a separate Simulation document, which will be made available on the SNAP website.

11.1 Description of trial simulator and parameters

The trial design is described in the SNAP core protocol. The primary estimand, primary model and prior distributions for primary model parameters are described in Sections 6.1, 7.1 and 8 of this appendix, respectively. These trial simulations are generated for three silos and three domains, each with two interventions, as illustrated in Section 3.1 of this appendix. The trial simulator's decision quantities, decision thresholds and subsequent adaptations are documented in Section 9 and 10 of this appendix.

There are assumptions that are made in the simulations, but are not specific to the trial designs. The following assumptions are made for the simulations:

- No drop-outs or missing data and every participant is eligible for each domain (every site participating in every domain), except EOS where 45% of participants are never eligible.
- Full accrual within a 4-year period (slow ramp-up period, then steady 31 adult participants/week and ~5 paediatric participants/week).
- Prevalence of PSSA is 16%, of MSSA is 64% and of MRSA is 20% in adult and paediatric groups.
- Baseline mortality rates of 15% in PSSA silo, 15% in MSSA silo and 20% in MRSA silo for adults and ~3% for children across all silos.
- Proportion eligible for EOS is 10% by platform Day 7 and 45% by platform Day 14.
- Interims start when 500 participants (adult and paediatric subpopulations combined) have 'complete' data (i.e., follow up until platform Day 90) and are then performed each additional 500 participants, with complete data known for all participants.
- Changed allocation following a domain conclusion to reflect a 75% subsequent uptake of the non-inferior or superior intervention.
- The trial is perpetual but the simulations are halted when there are 6000 adult and 1000 paediatric participants enrolled.
- The mortality rate as a function of the domain and silo are assumed in each simulation scenario, which are summarised below.
- Between 2,000-10,000 trials simulated for each plausible outcome scenario (see Section 11.2).

11.2 Simulation parameters and scenarios

Six scenarios are highlighted to illustrate possible, although not necessarily expected, trial outcomes (see next page) in the adult and paediatric subpopulations. These range from the null models for superiority and non-inferiority across domains and silos, where all odds ratios ($\boldsymbol{\beta_{a,s,d_k}}$) are 1.0 and 1.2, respectively (scenarios 1-2), to consistent moderate (OR=0.75) and large (0.55) reductions in mortality (OR=0.55) across all domains and silos (scenarios 3-4) in each subpopulation. Reverse direction of effects in adult compared to paediatric subpopulations are not anticipated, however, these are illustrated in scenarios 5 and 6. Trial operating characteristics from simulations for other scenarios may be available in supporting documentation on the trial website. Trial data was generated for these six scenarios, based on parameters values detailed in Section 11.1 and the trial primary estimand (Section 6.1), primary model (Section 7.1) and prior distributions (Section 8). In addition, four combinations of decision thresholds (see options 1-4 below) were explored,

however, only option 1 provided adequate control of the type 1 error (false positive declarations), whilst maintaining high statistical power (true positive declarations of superiority or non-inferiority).

Decision criteria	Option 1 Thresholds	Option 2 Thresholds	Option 3 Thresholds	Option 4 Thresholds
Declaring non-inferiority	0.99	0.99	0.975	0.975
Declaring superiority	0.99	0.99	0.975	0.975
Declaring futility for non-inferiority	0.01	0.05	0.01	0.05
Declaring futility for superiority	0.01	0.05	0.01	0.05

Simulation Scenario	Silo	Domain A Odds Ratio Adult Child	Domain B Odds Ratio Adult Child	Domain C Odds Ratio Adult Child	Description of scenario
1	PSSA MSSA MRSA	1.00 1.00 1.00 1.00 1.00 1.00	1.00 1.00 1.00 1.00 1.00 1.00	1.00 1.00 1.00 1.00 1.00 1.00	Null scenario for superiority across all domains for all silos and subpopulations
2	PSSA MSSA MRSA	1.20 1.20 1.20 1.20 1.20 1.20	1.00 1.00 1.00 1.00 1.00 1.00	1.20 1.20 1.20 1.20 1.20 1.20	Null scenario for superiority in domain B & boundary of non-inferiority in domains A & C for all silos and subpopulations
3	PSSA MSSA MRSA	0.75 0.75 0.75 0.75 0.75 0.75	0.75 0.75 0.75 0.75 0.75 0.75	0.75 0.75 0.75 0.75 0.75 0.75	Moderate reduction in mortality across all domains for all silos and subpopulations
4	PSSA MSSA MRSA	0.55 0.55 0.55 0.55 0.55 0.55	0.55 0.55 0.55 0.55 0.55 0.55	0.55 0.55 0.55 0.55 0.55 0.55	Large reduction in mortality across all domains for all silos and subpopulations
5	PSSA MSSA MRSA	1.20 0.75 1.20 0.75 1.20 0.75	1.00 0.75 1.00 0.75 1.00 0.75	1.20 0.75 1.20 0.75 1.20 0.75	Boundary of non-inferiority for adults in domains A & C, null model for adult superiority in domain B and moderate reductions in paediatric domains A, B & C
6	PSSA MSSA MRSA	0.75 1.20 0.75 1.20 0.75 1.20	0.75 1.00 0.75 1.00 0.75 1.00	0.75 1.20 0.75 1.20 0.75 1.20	Boundary of non-inferiority for paediatric domain A & C, null model for paediatric superiority in domain B and moderate reductions in adult domains A, B & C

11.3 Trial operating characteristics (including average sample size, type 1 error and power)

For each scenario and decision threshold option 1 (defined in Section 11.2), trial operating characteristics were calculated based on between 2,000-10,000 simulations. The proportion of trials declaring (i) non-inferiority, (ii) superiority, (iii) futility for non-inferiority and (iv) futility for superiority are presented in Table 1. **To control the type 1 error rate to less than 7%, a non-inferiority and superiority threshold of 0.99 and a futility threshold (for both non-inferiority and superiority) of 1% is used in the SNAP platform. The platform is adequately powered to declare non-inferiority and/or superiority for moderate effect sizes, according to decision rules documented in either the DSA's or Section 9 of the statistical appendix.**

Table 1: Proportion of simulated trials declaring non-inferiority, superiority or futility for each domain

		Non-inferiority			Superiority			Futility for non-inferiority			Futility for superiority		
Scenario	**Silo**	**A**	**B***	**C**	**A**	**B***	**C**	**A**	**B***	**C**	**A**	**B***	**C**
1	PSSA	0.22	NA	0.22	0.05	0.06	NA	0.00	NA	0.00	0.00	0.69	NA
	MSSA	0.46	NA	0.47	0.06	0.06	NA	0.01	NA	0.00	0.07	0.69	NA
	MRSA	NA	NA	0.26	0.06	0.06	NA	NA	NA	0.00	0.28	0.69	NA
2	PSSA	0.06	NA	0.03	0.01	0.07	NA	0.04	NA	0.01	0.00	0.72	NA
	MSSA	0.02	NA	0.07	0.00	0.07	NA	0.07	NA	0.05	0.04	0.72	NA
	MRSA	NA	NA	0.04	0.01	0.07	NA	NA	NA	0.03	0.70	0.72	NA
3	PSSA	0.61	NA	0.78	0.30	0.92	NA	0.00	NA	0.00	0.00	0.01	NA
	MSSA	0.99	NA	0.95	0.76	0.92	NA	0.00	NA	0.00	0.00	0.01	NA
	MRSA	NA	NA	0.84	0.40	0.92	NA	NA	NA	0.00	0.03	0.01	NA
4	PSSA	0.83	NA	0.95	0.63	1.00	NA	0.00	NA	0.00	0.00	0.00	NA
	MSSA	1.00	NA	1.00	0.99	1.00	NA	0.00	NA	0.00	0.00	0.00	NA
	MRSA	NA	NA	0.98	0.81	1.00	NA	NA	NA	0.00	0.00	0.00	NA
5	PSSA	0.06	NA	0.02	0.01	0.08	NA	0.05	NA	0.01	0.00	0.70	NA
	MSSA	0.02	NA	0.07	0.00	0.08	NA	0.07	NA	0.04	0.04	0.70	NA
	MRSA	NA	NA	0.04	0.01	0.08	NA	NA	NA	0.02	0.70	0.70	NA
6	PSSA	0.62	NA	0.76	0.30	0.91	NA	0.00	NA	0.00	0.00	0.01	NA
	MSSA	0.98	NA	0.94	0.73	0.91	NA	0.00	NA	0.00	0.00	0.01	NA
	MRSA	NA	NA	0.83	0.45	0.91	NA	NA	NA	0.00	0.02	0.01	NA

NA: not an appropriate decision criterium for the domain-silo combination.

*: Domain B combined over all silos