Domain-Specific Appendix:

Backbone Domain: MRSA Silo

Dapto-SNAP Supplement

Staphylococcus aureus **Network Adaptive Platform trial (SNAP)**

MRSA Treatment Domain-Specific Appendix DAPTO-SNAP Supplement Version 1.0 dated 08 December 2023

Summary

This document describes the optional DAPTO-SNAP supplement to the current version of the MRSA DSA. Specifically, this is a nested 300 patient randomized controlled trial of daptomycin vs. vancomycin being conducted within the MRSA domain. It is designed to be read in combination with the core protocol AND backbone MRSA domain specific appendix.

At this participating site, the following interventions have been selected within this nested study:

☐ Intravenous vancomycin or daptomycin by randomization (DAPTO-SNAP)

It is important to note that all patients may also be eligible for randomization to adjunctive cefazolin vs. no cefazolin in the MRSA Domain including those who are excluded from DAPTO-SNAP due to inability to take one of vancomycin or daptomycin may remain eligible for the overall MRSA domain.

SNAP: DAPTO-SNAP Summary	
Interventions	● Intravenous vancomycin OR daptomycin See text for dosing, including adjustments for renal function.
Silos, domains, and cells	Platform eligible participants within the MRSA silo in the DAPTO-SNAP nested trial will be analysed. The direct comparisons between the effect of vancomycin versus daptomycin as the backbone anti-MRSA therapy on study outcomes will be estimated and reported.
Evaluable treatment-by-treatment interactions	Treatment-treatment interactions are considered possible between the backbone of daptomycin or vancomycin and the assignment to cefazolin or no cefazolin within this cell as well as to the receipt of adjunctive clindamycin or no clindamycin.
Randomisation	Randomization to daptomycin vs. vancomycin will happen at platform entry at participating DAPTO-SNAP sites, and this allocation will only be revealed if eligibility criteria for this comparison are met. If eligibility criteria are not met, patients may still receive investigator's choice daptomycin vs. vancomycin and participate in the cefazolin vs no cefazolin allocation as described in the MRSA DSA.
Specific Inclusions	Inclusion criteria are the same as the Platform (see Core Protocol Section 6.5) And the MRSA backbone domain
Specific Exclusions	Patients will be excluded from this domain if they meet any of the following additional criteria at the time of domain eligibility assessment: 1. Severe allergy or non-severe rash to vancomycin OR daptomycin 2. Suspected or confirmed MRSA pneumonia 3. Known vancomycin MIC ≥2mg/L or daptomycin MIC ≥1mg/L
Endpoints	The primary outcome for DAPTO-SNAP is a 90-day Desirability of Outcome Ranking (DOOR) as defined in the SNAP core protocol and is based on a

	modified version of the Antibiotic Leadership Research Group (ALRG) DOOR (see 8.5.1). DAPTO-SNAP- specific Secondary outcomes: • Each component of the DOOR will be separately reported. • Drug induced myositis (creatinine kinase ≥5 times the upper limit of normal occurring while on daptomycin or vancomycin therapy up to day 42 from platform entry
Decision criteria	DAPTO-SNAP: The study is powered for a superiority comparison based on the primary objective, a comparison of DOOR outcomes. The probability of a subject from the daptomycin arm having a superior DOOR ranking relative to a subject from the vancomycin arm will be calculated along with a 95% confidence interval. Superiority will be considered to have been achieved if the 95% confidence interval for probability of having a superior DOOR ranking with daptomycin does not cross 50%. If the confidence interval crosses 50% however, the null hypothesis cannot be rejected. Sample size was calculated on the basis of the primary hypothesis. Assuming a 60% probability of a better DOOR in the daptomycin treatment group versus the vancomycin treatment group, with 80% power and alpha=0.025 (by one-sided Wilcoxon rank sum test), 131 participants would be required in each treatment group. Allowing for up to 12.5% dropout we plan to recruit 150 patients per arm (300 subjects in total).
Pre-specified secondary analyses	DAPTO-SNAP: In addition to sub-groups already in the MRSA Domain Specific Appendix, pre-specified secondary analysis will be performed to look at the following subgroups by stratification: 1. Receipt of (randomized) adjunctive cefazolin or not 2. An analysis stratified by vancomycin MICs (as centrally adjudicated) will be performed subsequent to the main trial publication

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1. ABBREVIATIONS

See Core Protocol and MRSA Domain Specific Appendix.

2. PROTOCOL APPENDIX STRUCTURE

This supplement is nested under the MRSA domain specific appendix. It exists to describe the DAPTO-SNAP nested trial which will be conducted on the platform and will likely complete (by virtue of fixed sample size) prior to the MRSA domain. The reader should be familiar with that domain specific appendix and with the overall rationale of the platform.

The current version of the Core Protocol, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (https://www.snaptrial.com.au/).

3. MRSA TREATMENT DOMAIN-SPECIFIC APPENDIX VERSION

The version of the MRSA Treatment Domain-Specific Appendix DAPTO-SNAP supplement is in this document's header and on the cover page.

Todd C Lee wrote the first draft of this appendix.

3.1. Version history

Version 1.0: Approved by the MRSA Domain-Specific Working Group (DSWG) on the 07 February 2024.

4. MRSA TREATMENT DOMAIN GOVERNANCE

4.1. Domain members

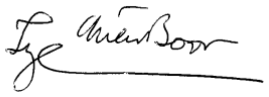
See MRSA Domain Specific Appendix.

4.2. Contact Details

See MRSA Domain Specific Appendix.

5. MRSA TREATMENT DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The MRSA Treatment Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official MRSA Treatment Domain-Specific Appendix for the SNAP trial. Signed on behalf of the committee,

Chair  Date 07 February 2024

David Lye

6. BACKGROUND AND RATIONALE

6.1. DAPTO-SNAP trial definition

Nested within the above overarching goal is a direct randomized comparison of daptomycin vs. vancomycin for participating hospital sites (DAPTO-SNAP).

6.2. Background on MRSA backbone therapy

MRSA infections result in higher crude mortality than MSSA infections (1, 2). The current standard therapy in many centres for MRSA-B is vancomycin. Compared with β-lactams, vancomycin kills MSSA more slowly, has less penetration of infected tissue (3), and in observational studies is associated with poorer patient outcomes (2). Alternative agents to vancomycin have become available, including daptomycin, ceftobiprole and ceftaroline. However, daptomycin, ceftobiprole and ceftaroline have not been demonstrated to be superior to vancomycin for MRSA-B (4) and newer agents are, such as ceftobiprole are prohibitively expensive.

Vancomycin has been the standard of care for MRSA bacteremia for decades (5) but it has several disadvantages including the risk of acute kidney injury and challenging pharmacology requiring therapeutic drug monitoring and dose adjustments using specialized software and/or expert pharmacy support(6). An important comparative effectiveness question therefore arises: can we replace vancomycin with another agent to overcome vancomycin's shortcomings? Daptomycin offers several potential advantages with less risk of acute renal failure, no requirement for therapeutic drug

monitoring, and it can be given as a single dose per day (vs up to 4/day for vancomycin) requiring less nursing and pharmacy time. Daptomycin (now generic in many countries) remains more expensive than vancomycin (excluding administration and monitoring costs), and its use remains infrequent since daptomycin has not been demonstrated to be superior. There have been only 99 patients in RCTs directly comparing these two drugs in MRSA bacteremia (7). Other observational comparisons are favorable (8), but they are subject to confounding and immortal time bias (9). For most centres in SNAP, the choice of daptomycin or vancomycin is left up to the treating team. At participating hospitals, we will nest a head-to-head randomized comparison between these two drugs to provide additional comparative effectiveness data in MRSA bacteremia.

7. DAPTO-SNAP OBJECTIVES

The objective of this nested trial is to directly compare daptomycin to vancomycin as the backbone therapy for eligible MRSA-B. We hypothesize that within the directly randomized comparison, that daptomycin will have a superior probability of attaining a higher DOOR outcome (see below) at day 90.

8. TRIAL DESIGN

This domain will be conducted as part of the SNAP trial (see Core Protocol Section 6 and MRSA DSA). Treatment allocation for DAPTO-SNAP will both be at a fixed 1:1 ratio, as described in the Core Protocol Section 6.7.

8.1. Population

Patients with Methicillin-resistant *S. aureus* bacteraemia admitted to a participating hospital.

8.2. Eligibility criteria

Patients are eligible for this nested trial if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 6.5) AND all of the cell-level inclusion and none of the cell-level exclusion criteria AND all of the additional DAPTO-SNAP eligibility criteria. Patients eligible for SNAP may have conditions that exclude them from DAPTO-SNAP.

8.2.1. Cell inclusion criteria

- As per the SNAP MRSA domain specific appendix (MRSA confirmed microbiologically)

8.2.2. Cell exclusion criteria

Patients will be excluded from DAPTO-SNAP if they have any of the following:

1. Severe allergy or non-severe rash to vancomycin OR daptomycin
    - Vancomycin infusion reaction (formerly known as “red man syndrome”) is due to direct histamine release and is not generally an allergy, and therefore is not considered an exclusion.
2. Suspected or confirmed MRSA pneumonia (daptomycin is inactivated by pulmonary surfactant. Septic pulmonary emboli from presumed right sided endocarditis or central line infection are not in themselves an exclusion)
3. Known vancomycin MIC ≥2mg/L or daptomycin MIC ≥1mg/L

8.3. Interventions

- Intravenous vancomycin or daptomycin as randomized

8.3.1. Vancomycin dosing

Sites may follow local guidelines for the use of vancomycin. These are described in section 8.3.1 of the MRSA DSA.

8.3.2. Daptomycin dosing

Daptomycin is registered for use at 6mg/kg per day in most countries. The dose prescribed by the treating teams should not be less than the monograph dose [accounting for renal adjustment]. Many (if not most) experts now advise 8-10mg/kg per day for serious infections such as MRSA bacteraemia (10-13).

The suggested adjustment for renal function for the higher doses are:

Creatinine clearance [NB1] (mL/min)	**Daptomycin Dose**
>30ml/min	8-10mg/kg IVI q24h
< 30ml/min	8mg/kg q48h IVI
On continuous renal replacement therapy	8mg/kg q48h IVI
On haemodialysis	8mg/kg q48h IVI, dose after dialysis

NB1: Use the Cockcroft-Gault formula or online calculator to approximate creatinine clearance (e.g., on MDCalc).

Doses should be rounded to the nearest 50mg and use adjusted body weight (e.g, on MDCalc) for obesity (14).

It is recommended that holding or reducing the dose of **primary prevention** statins (particularly rosuvastatin or atorvastatin ≥40mg/day) be considered while on daptomycin. This is a clinical decision and not a trial requirement.

8.3.3. Timing of initiation of MRSA Backbone therapy

Trial antibiotic(s) should be initiated as soon as possible following reveal of treatment allocation. If already receiving vancomycin or daptomycin, the timing of the next dose should be at the recommended interval from the last dose. If changing from vancomycin to daptomycin, the first dose of daptomycin should be administered as soon as possible. If switching from daptomycin to vancomycin, the first dose should follow section 8.3.1 of the MRSA DSA or local standard of care.

8.3.4. Duration of administration of MRSA Backbone therapy

The duration of vancomycin or daptomycin is guided by local guidelines and practice for methicillin-resistant *Staphylococcus aureus* bacteraemia. The intention is for treatment with the allocated drug for the duration of IV therapy. Participation in the early oral switch domain is allowed.

8.4. Concomitant care

If broadening of antibiotic therapy is clinically indicated, non-β-lactam antibiotics are preferred (e.g., gram negative coverage may be provided with ciprofloxacin or aminoglycoside, and anaerobic coverage with metronidazole). Ceftaroline or ceftobiprole should not be used within the first 14 days.

8.5. Additional DAPTO-SNAP specific Endpoints

8.5.1. Primary endpoint

The primary outcome is a 90-day Desirability of Outcome Ranking #1 (DOOR; modified ARLG version) as defined in the core protocol with ties broken by the modified functional bloodstream infection score (FBIS).

Modified ARLG DOOR:

Rank	**Alive at 90 days**	**How many of:** • **Microbiological treatment failure** • **Infectious Complication*** • **Any SAR OR AE leading to study drug discontinuation****	**QoL**
1	Yes	0 of 3	

2	Yes	1 of 3	Tiebreaker based on the modified FBIS
3	Yes	2 of 3	
4	Yes	3 of 3	
5	No	Any	

*New metastatic focus OR change in antibiotic due to inadequate clinical response. Change in antibiotic due to inadequate clinical response will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains.

**Any SAR (core 2ry endpoint) OR change in antibiotic due to AE. Change in antibiotic due to adverse event will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains.

Modified FBIS:

Rank	Description
4	Out of hospital; able to complete daily activities without assistance
3	Out of hospital; unable to complete daily activities without assistance
2	Out of hospital; significant disability; requires a high level of care and assistance daily (this includes residential aged care)
1	Hospitalised (or equivalent, such as hospice)

8.5.2.Secondary endpoints

- All secondary platform endpoints as specified in the Core Protocol Section 6.8.
- Each component of the DOOR (see Core Protocol Section 6.8.2.12 for definitions). Of these death and microbiological treatment failure are already specified core protocol secondary endpoints. Additional components to be included as DAPTO-SNAP specific endpoints are:
    - Infectious Complication: New metastatic focus OR change in antibiotic (daptomycin or vancomycin) due to inadequate clinical response. Change in antibiotic due to inadequate clinical response will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains.
    - Any SAR OR AE leading to study drug (daptomycin or vancomycin) discontinuation: Change in antibiotic due to adverse event will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains
- Drug induced myositis (creatinine kinase ≥5 times the upper limit of normal occurring while on therapy with daptomycin or vancomycin up to day 42 from platform entry; e.g., CTCAE grade 3+). The upper limit of normal for creatinine kinase is 180 U/L in females and 200 U/L in males.

There will also be a formal economic analysis for DAPTO-SNAP conducted with expert healthcare economists and further delineated at that time.

9. TRIAL CONDUCT

9.1. DAPTO-SNAP-specific data collection

9.1.1. Microbiology

No additional microbiological testing is needed.

9.1.2. Clinical data and sample collection

Additional study-specific data will be collected in addition to that specified in the MRSA DSA:

- Daptomycin daily dose in mg (if applicable)
- Patient ideal weight in kg (or weight and height of patient to calculate ideal weight)
- Serum creatinine kinase (known as CPK or CK in various regions) at study entry, once within the first 7 days, and then weekly while on MRSA backbone therapy with vancomycin or daptomycin up to day 42 from platform entry. This will be collected in all patients even those assigned to vancomycin. Additional testing may be performed if there is clinical suspicion of myositis while on vancomycin or daptomycin.

9.1.3. DAPTO-SNAP-specific study timeline

Please see Table 3 for the DSA timeline. The only addition is a CK level on study entry, within the first 7 days, and then weekly while on therapy, up to day 42 from platform entry.

9.1.4. DAPTO-SNAP-specific study visit day details

All core study visit details are specified in the Core Protocol (Section 8.8). Data will be collected, as per the CRFs, on platform day 1, day 8-10 (for data from platform days 1-7), day 15-18 (for data from platform days 8-14), day 28, day 42, day 90, and acute and total discharge.

Additional domain-specific study procedures are outlined below.

9.1.4.1. Day 1-3 (screening for eligibility)

In addition to the screening procedures outlined in the Core Protocol (Section 8.8), additional domain-specific screening procedures will occur as per the eligibility criteria outlined in Section 8.2.

9.1.4.2. Day 1-7

In addition to the activities outlined in the Core Protocol (Section 8.8) additional domain-specific activities will be conducted, including:

- Ensuring appropriate dosing and administration of study drugs

9.1.4.3. Days 2, 5, 14

Core activities during the first 14 days from platform entry are outlined in the Core Protocol (Section 8.8). MRSA domain specific activities are described in the MRSA DSA section 9.1.4.3

Additional DAPTO-SNAP-specific activities will be conducted, including:

- Reviewing and recording patient progress in relation to safety events and changes to the allocated antibiotic regimen during platform days 1-14

- Ensuring serum creatinine kinase should be measured on enrolment, once on days 1-7, weekly or if there is clinical suspicion of myositis while on vancomycin or daptomycin therapy up to day 42 from platform entry

9.1.4.4. Day 90

These activities are outlined in the Core Protocol (Section 8.8) and the MRSA domain specific appendix.

9.2. Criteria for discontinuation

Refer to Core Protocol Section 8.10 and MRSA DSA Section 9.2 for criteria for discontinuation of participation.

9.3. Blinding

9.3.1. Blinding

See MRSA DSA Section 9.3.1.

9.3.2. Unblinding

See MRSA DSA Section 9.3.2.

10.STATISTICAL CONSIDERATIONS

10.1. Estimands, endpoints, and intercurrent events

10.1.1. Primary estimand

DAPTO-SNAP will have a separate statistical analysis plan which will be approved prior to completion of 25% enrolment (i.e. n=75). Based on available funding and sample size estimates for the desired effect size, DAPTO-SNAP has a sample size limit of 300 completed patients worldwide.

The DOOR outcome is defined in 8.5.1 with ties broken by modified FBIS.

The study is powered for a superiority comparison based on the primary objective, a comparison of DOOR outcomes. The probability of a subject from the daptomycin arm having a superior DOOR ranking relative to a subject from the vancomycin arm will be calculated along with a 95% confidence interval. Superiority will be considered to have been achieved if the 95% confidence interval for probability of having a superior DOOR ranking with daptomycin does not cross 50%. If the confidence interval crosses 50% however, the null hypothesis cannot be rejected.

Sample size was calculated on the basis of the primary hypothesis. Assuming a 60% probability of a better DOOR in the daptomycin treatment group versus the vancomycin treatment group, with a 80% power and alpha=0.025 (by one-sided Wilcoxon rank sum test), 131 participants would be required in each treatment group. Allowing for up to 12.5% dropout we plan to recruit 150 patients per arm (300 subjects in total).

10.1.2. Secondary estimands

All core secondary estimands, endpoints, and intercurrent events strategies are specified in the Statistical Analysis Appendix.

The DAPTO-SNAP-specific secondary estimands, endpoints, and intercurrent events are defined as follows:

Estimand/Objective/Target population	Endpoint/Population-level summaries	Intercurrent events strategy
Estimand A2.9.1 To evaluate, within the MRSA cell, the effect of the revealed randomised intervention compared to the MRSA	Endpoint: See Core Protocol Section 6.8.2.12 The DOOR is a hierarchical ordinal outcome that allows a ranking of	Treatment policy strategy (intent-to-treat principle)

cell control, on the probability of **a more desirable DOOR at 90 days** after **platform entry**, in DAPTO-SNAP enrolled participants.	patients on the desirability of each outcome. There are 5 ordered outcomes, and tie-breakers for survivors with a 4 scale functional outcome. Therefore, there are 17 outcomes (death is always the worst). Population summary: The probability of having a better outcome on the DOOR for the Daptomycin arm will be presented with 95% confidence intervals for DAPTO-SNAP enrolled participants. The calculation is based on the Wilcoxon-Mann-Whitney U test.	
Estimand A2.9.2 To evaluate, within the MRSA cell, the effect of the revealed randomised intervention compared to the MRSA cell control, on the probability of **a more desirable DOOR at 90 days** after **platform entry**, in DAPTO-SNAP enrolled participants.	Endpoint: See Core Protocol Section 6.8.2.12 The DOOR is a hierarchical ordinal outcome that allows a ranking of patients on the desirability of each outcome. There are 5 ordered outcomes, and tie-breakers for survivors with a 4 scale functional outcome. Therefore, there are 17 outcomes (death is always the worst). Population summary: The probability of having a better outcome on the DOOR for the Daptomycin arm will be presented with 95% confidence intervals for DAPTO-SNAP enrolled participants. The calculation is based on the Wilcoxon-Mann-Whitney U test.	Principal stratum policy (per protocol principle)
Estimand A2.9.3 To evaluate, within the MRSA cell, the effect of the revealed randomised intervention compared to the MRSA cell control, on the proportional odds ratio of DOOR at platform Day 90, in DAPTO-SNAP enrolled participants.	Endpoint: See Core Protocol Section 6.8.2.12 The DOOR is a hierarchical ordinal outcome that allows a ranking of patients on the desirability of each outcome. There are 5 ordered outcomes, and tie-breakers for survivors with a 4 scale functional outcome. Therefore, there are 17 outcomes (death is always the worst). Population summary: Log proportional odds ratio of intervention compared to domain control for being in DOOR group j or higher compared to group j-1 or lower, for DAPTO-SNAP enrolled participants.	Treatment policy strategy (intent-to-treat principle)
Estimand A2.9.4 To evaluate, within the MRSA cell, the effect of the revealed randomised intervention compared to the MRSA cell control, on the proportional odds ratio of DOOR at platform Day 90, in DAPTO-SNAP enrolled participants.	Endpoint: See Core Protocol Section 6.8.2.12 The DOOR is a hierarchical ordinal outcome that allows a ranking of patients on the desirability of each outcome. There are 5 ordered outcomes, and tie-breakers for survivors with a 4 scale functional	Principal stratum policy (per protocol principle)

	outcome. Therefore, there are 17 outcomes (death is always the worst). Population summary: Log proportional odds ratio of intervention compared to domain control for being in DOOR group j or higher compared to group j-1 or lower, for DAPTO-SNAP enrolled participants.	
Estimand A2.9.5 To evaluate, within the MRSA cell, the effect of revealed randomised intervention compared to the MRSA cell control, on probability of an infectious complication **in the 90 days following platform entry**, in DAPTO-SNAP enrolled participants.	Endpoint: Infectious complication defined as New metastatic focus OR change in antibiotic due to inadequate clinical response. Change in antibiotic due to inadequate clinical response will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains. Population summary: Log-odds ratio of the stated event between intervention and control groups within each relevant cell.	Treatment policy strategy (intent-to-treat principle)
Estimand A2.9.6 To evaluate, within the MRSA cell, the effect of revealed randomised intervention compared to the MRSA cell control, on probability of any SAR OR AE leading to study drug discontinuation (in this case, refers to daptomycin or vancomycin), in DAPTO-SNAP enrolled participants..	Endpoint: any SAR OR AE leading to study drug discontinuation. Change in daptomycin or vancomycin due to adverse event will be determined using only data already collected as part of the backbone (up to day 14) and EOS (up to day 28) domains. Population summary: Log-odds ratio of the stated event between intervention and control groups within each relevant cell.	Treatment policy strategy (intent-to-treat principle)
Estimand A2.9.7 To evaluate, within the MRSA cell, the effect of revealed randomised intervention compared to the MRSA cell control, on the probability of drug induced myositis (creatinine kinase ≥5 times the upper limit of normal occurring while on therapy), in DAPTO-SNAP enrolled participants.	Endpoint: Creatinine kinase ≥5 times the upper limit of normal, as measured any time up to day 42 from platform entry. Upper limit of normal is 180 U/L in females and 200 U/L in males. Population summary: Log-odds ratio of the stated event between intervention and control groups within each relevant cell.	Treatment policy strategy (intent-to-treat principle)

10.2. Statistical modelling

10.2.1. Primary model

DAPTO-SNAP will have a separate statistical analysis plan which will be approved formally prior to completion of 25% enrolment.

10.2.2. Secondary models

DAPTO-SNAP will have a separate statistical analysis plan which will be approved formally prior to completion of 25% enrolment.

10.3. Decision criteria

DAPTO-SNAP will have a separate statistical analysis plan which will be approved formally prior to completion of 25% enrolment. There will be no pre-planned interim analyses as a negative study at full sample size will make a meaningful contribution.

10.4. Randomisation

Participants will be randomised at platform entry in a fixed 1:1 ratio. A patient's allocated intervention will be revealed at the time that both MRSA is microbiologically identified, and domain and silo specific eligibility criteria are confirmed.

10.5. Interactions with domains

An *a priori* interaction with the adjunctive antibiotic domain and with the MRSA domain (cefazolin vs. no cefazolin) is considered possible and will be incorporated into the statistical models used to analyse this domain. To protect the integrity of the MRSA backbone antibiotic domain (cefazolin vs no cefazolin), the mortality numbers or treatment effect as a function of cefazolin exposure will not be disclosed if DAPTO-SNAP finishes prior to the MRSA backbone antibiotic domain.

10.6. Pre-specified secondary analyses

In addition to sub-groups already in the MRSA Domain Specific Appendix Section 10.6, pre-specified secondary analysis will be performed to look at the following subgroups by stratification:

1. Receipt of (randomized) cefazolin or not. The individual categories of the DOOR will not be stratified by cefazolin exposure to protect the integrity of the MRSA backbone adjunctive cefazolin trial (unless it has already completed). The treatment effect of daptomycin vs vancomycin according to allocation to cefazolin vs no cefazolin may only be reported if it doesn't reveal outcomes or treatment effect of cefazolin vs no cefazolin.
2. An analysis stratified by vancomycin MICs (as centrally adjudicated) will be performed subsequent to the main trial publication

10.7 Principal stratum policy

The principal stratum policy (also known as a 'per protocol principle') for Estimand A2.9.2 uses the population as described below:

Treatment as assigned until the prescribed total duration of therapy unless discontinuation due to adverse drug event, change to oral step-down therapy, or death. Per protocol will be defined as:

1) Receiving at least one dose of allocated drug per day from domain entry on at least 75% of days (rounded up to the nearest whole day) where a backbone intravenous drug is given for the index episode of MRSA bacteraemia.
    a. E.g., For those allocated to oral switch at day 7, at least 5 days; at day 14, at least 12 days. For those who receive clinician determined duration of IV therapy, 75% of that – e.g if 28 days, then at least 21 days. If 42 days, then at least 32 days.

    AND

    b. One or more doses per day of the non-allocated IV therapy (vancomycin if allocated to daptomycin; daptomycin if allocated to vancomycin) was received on less than two days between domain entry and acute hospital discharge.

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Committee

The DSMC will monitor for safety events. There are no pre-planned interim analyses as a negative study at full sample size will make a meaningful contribution.

11.2. Potential domain-specific adverse events

All treatment-related adverse events of particular interest for patients in this domain and silo are captured in the secondary endpoints (Section 8.5.2).

Other serious adverse reactions (SARs) should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core protocol Section 10).

11.3. Domain-specific consent issues

Consent for this domain will be sought at platform entry and will not require re-confirmation or repeat eligibility assessment at the time susceptibility is confirmed.

12.GOVERNANCE ISSUES

12.1. Funding of DAPTO-SNAP

DAPTO-SNAP has received additional funding from the Canadian Institutes of Health Research (#474605). Canadian participating sites will receive payment from the Research Institute of the McGill University Health Centre. International participating sites will receive payment via the University of Melbourne (with a separate financial arrangement negotiated between RI-MUHC and University of Melbourne).

12.2. Funding of domain interventions and outcome measures

Outcome measures are pragmatic and do not deviate from routine testing performed during usual care for SAB. Within DAPTO-SNAP there is funding to partly or fully offset pharmacy wholesale cost differences between vancomycin and daptomycin depending on local acquisition costs. It is expected that each participating site will come up with their own internal cost structure – these will not be negotiated centrally.

12.3. Domain-specific declarations of interest

All investigators involved in SNAP maintain a registry of interests on the SNAP website.

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