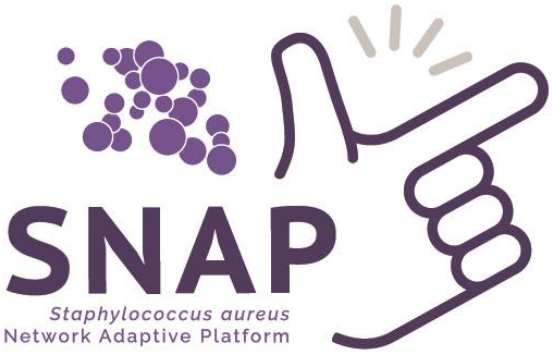

Paediatric and Youth-Specific Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP-PY)

Paediatric-Specific Appendix Version 2.0 dated 24 March 2023

Summary

This is an appendix within SNAP that aims to:

- Describe adaptations to the Core Protocol in order to test paediatric outcomes in hospitalised children with SAB.

SNAP: Synopsis of paediatric specific protocol adaptations	
	SNAP PROTOCOL
TITLE	*Staphylococcus aureus* Network Adaptive Platform trial in Paediatric and Youth (SNAP-PY)
BACKGROUND	*Staphylococcus aureus* bacteraemia (SAB) is a common and severe infection, with one in three children experiencing the composite of: length of stay >30 days (26%), ICU admission (20%), relapse (4%), or death (3%), despite current best available therapies. We are using an adaptive platform trial to allow us to simultaneously investigate the optimal treatments for the management of SAB. The trial will include 3 silos (PSSA, MSSA, and MRSA). We plan to test interventions within 3 initial domains, with the potential to add further domains to the platform.
ENDPOINTS	Primary platform endpoint: All-cause mortality 90 days from platform entry. Secondary core platform endpoints: refer to Core Protocol Section 6.8, in some cases minor modifications are made (see section 7.2.2). Secondary paediatric-specific endpoints: The paediatric composite outcome will include a composite of 4 variables collected as secondary outcomes across the trial that have been shown in the ISAIAH study (1) to be useful outcome measures. The chosen outcomes include mortality, markers of relapse and extended hospitalisation. 1. Mortality by day 90 following platform entry 2. Microbiological treatment failure defined as positive sterile site culture for *S. aureus* (of the same silo as the index isolate) between 14 and 90 days after platform entry 3. Diagnosis of new foci between 14 and 90 days after platform entry 4. Length of total index hospitalisation of >30 days from the time of platform entry. Total index hospitalisation is defined as a continuous admission to any healthcare facility, including rehabilitation hospitals, and hospital-in-the-home or outpatient parenteral antimicrobial therapy services. If an event is observed in any of the four endpoints, then the composite endpoint will be considered to have been met.
PLATFORM SPECIFIC INCLUSIONS	These are the same as for the overall Core Protocol Section 6.5. Participants meeting the following inclusion criteria will be eligible for SNAP-PY: 1. Age 0 to < 18 years of age.
PLATFORM SPECIFIC EXCLUSIONS	These are the same as for the overall Core Protocol Section 6.5.

STUDY DOMAINS	1. Antibiotic Backbone Domain 2. Adjunctive Treatment Domain 3. Early Oral Switch Domain 4. PET/CT Domain The default is that domain specific inclusion and exclusion criteria (see domain specific appendices) will apply to paediatric participants. In the early oral switch domain, the day 7 inclusion criteria is broadened to allow native bone and joint infections (see section 7.1).
NUMBER OF PARTICIPANTS	The initial trial funding and infrastructure will aim to enrol up to 6,000 adult participants with an additional 1,000 paediatric participants.
STATISTICAL CONSIDERATIONS	Statistical approaches are described in detail in the respective domain-specific appendices and the statistical analysis appendix. Paediatric participants will be randomised as a separate stratum into each domain according to the strategies outlined in the respective domain-specific appendices (DSAs; Section 10.4). Decision criteria for trial adaptations will be based on results obtained for the adult population only and according to what is stated in the domain-specific appendices (Section 10.3) and as detailed in the Statistical Appendix. Any pre-specified secondary analyses will be performed according to the strategies outlined in the respective domain-specific appendices (Section 10.6) and as detailed in the Statistical Appendix.

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1. ABBREVIATIONS

AHA	American Heart Association
ANZ	Australia and New Zealand
ASP	Anti-Staphylococcal Penicillin
CNS	Central Nervous System
COPAT	Complex Outpatient Parenteral Antimicrobial Therapy
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMC	Data and Safety and Monitoring Committee
eGFR	Estimated Glomerular Filtration Rate
EOS	Eosinophil
GTSC	Global Trial Steering Committee
HITH	Hospital In The Home
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
IV	Intravenous
LOS	Length of Stay
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin Susceptible *Staphylococcus aureus*
OPAT	Outpatient Parenteral Antibiotic Therapy
PICU	Paediatric Intensive Care Unit
PO	By mouth (Latin "per os")
PSSA	Penicillin Susceptible *Staphylococcus aureus*
PVL	Panton-Valentine Leucocidin
RAR	Response Adaptive Randomization
RCT	Randomised Controlled Trial
RSA	Region-Specific Appendix
SAB	*Staphylococcus aureus* Bacteraemia
SAE	Serious Adverse Event
TSST-1	Toxic Shock Syndrome Toxin 1

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both, and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models, including simulations to support trial design), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the Global Trial Steering Committee (GTSC) in conjunction with advice from the Statistical Subcommittee and the Data and Safety Monitoring Committee (DSMC).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It

is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

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. PAEDIATRIC-SPECIFIC APPENDIX VERSION

The version of the Paediatric and Youth-Specific Appendix is in this document's header and on the cover page.

3.1. *Version history*

Version 1: Approved by the SNAP-PY Working Group on 21 of JUNE 2021

Version 2: Approved by the SNAP-PY Working Group on 24 March 2023

4. PAEDIATRIC-SPECIFIC DOMAIN GOVERNANCE

4.1. *Members*

Chair(s): Associate Professor Asha Bowen

Members:
A/P Steven Tong
Dr Isabelle Malhamé
Dr Erica Hardy
Dr Anita Campbell
Dr Rachel Webb
Dr Emma Best
Dr Srinivas Murthy
Dr Amanda Gwee
Dr Philip Britton
Dr Lesley Voss
Dr Kevin Schwartz
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5. SNAP-PY WORKING GROUP AUTHORISATION

The SNAP-PY Working Group have read the appendix and authorise it as the official Paediatric and Youth-Specific Appendix for the study entitled SNAP. Signed on behalf of the committee,

Chair A/P Asha Bowen _____ Date 24/03/2023

6. BACKGROUND AND RATIONALE

6.1. *Introduction*

Staphylococcus aureus is one of the most common causes of clinically significant paediatric bacteraemia in the post-pneumococcal vaccine era, with authors of recent studies estimating the incidence of *S. aureus* bacteraemia in high-income countries between 6 - 26 / 100,000 children per year (2, 3). It is also the principal reason for admission to a paediatric intensive care unit (PICU) for management of sepsis in Australia and New Zealand (ANZ) (4). Despite this, <300 children worldwide have ever been randomly assigned into clinical trials to assess the efficacy of treatment of *S. aureus* bacteraemia (Appendix 1). Defining the optimal, comprehensive management strategies for *S. aureus* bacteraemia in children is of paramount importance, and forms the aims of SNAP-PY, which is achievable through inclusion of children into this multi-centre international adaptive platform clinical trial.

Treatment decisions for children with *S. aureus* bacteraemia, as with many other conditions, are largely guided by evidence from adults. In the SNAP trial we intend to collect and model data from children jointly with adult data (5). A key difference is the expected 90-day mortality in children is 2-3%, substantially less than that of adults at 15-20%. To power a paediatric-only trial of sufficient size to detect differences in 90-day mortality by treatment group would be infeasible by conventional standards.

The statistical model that will be used to analyse the SNAP data allows information about treatment efficacy to be shared (i.e. borrowed) between the adult and paediatric population. Trial stopping decisions for superiority, inferiority, or futility of treatments will be based on results from the larger adult population (with borrowing from the paediatric population). At the conclusion of trial domains (based on the adult data), the results for the paediatric population will also be examined and reported. Although the results from the adult population are likely to be less uncertain than the results from the paediatric population, understanding both results together in context will provide meaningfully useful clinical information. Therefore, the SNAP trial will provide substantially more rigour and evidence as to whether a treatment shown to be better in adults is also better in children. This model for generating evidence for paediatric is a significant advance over providing random care or extrapolating from adult populations to paediatric populations in the absence of trial data for children.

6.1.1. Antibiotic Backbone Domain

6.1.1.1. Penicillin vs (Flu)cloxacillin

There are no previously conducted randomised controlled trials (RCTs) available in adults or children addressing whether penicillin is favourable over an anti-staphylococcal penicillin (ASP) for penicillin susceptible *S. aureus* (PSSA) bacteraemia. This is despite 9% (49/465) of paediatric isolates confirmed to be PSSA in a recent prospective cohort of children with *S. aureus* bacteraemia from ANZ (Invasive *S. aureus* infections and hospitalisations in children [ISAIAH study] (1)). Two retrospective, propensity score-adjusted case-control analyses are available in adults from Denmark (6) (n=588) and ANZ (7) (n=915), comparing ASP or cefuroxime with penicillin for PSSA bacteraemia. Both studies reported a 30-day mortality benefit favouring penicillin, suggesting a potential benefit for benzylpenicillin therapy in patients with PSSA bacteraemia (6, 7).

Differing clinician opinions exist regarding the optimal management of patients with PSSA bacteraemia, with 70% of ANZ adult infectious diseases physicians surveyed opting to treat PSSA bacteraemia with the first-line agent, benzylpenicillin (8). This is also reflected in the lack of international guidelines specifically available for methicillin susceptible *S. aureus* (MSSA) or PSSA bacteraemia in children and adults. The American Heart Association (AHA) (9) recommend for paediatric MSSA endocarditis an ASP (nafcillin or flucloxacillin) and for PSSA endocarditis, penicillin. Australian guidelines recommend flucloxacillin or cefazolin for MSSA bacteraemia and penicillin for PSSA bacteraemia in both adults and children (10). Importantly these recommendations do not achieve Level A evidence (multiple populations evaluated, data from multiple RCT). Defining whether penicillin is favourable over an ASP for PSSA bacteraemia in children is a priority, given the lack of clinical trial evidence to inform this question, affecting approximately one in ten paediatric MSSA bacteraemia episodes.

6.1.1.2. Cefazolin vs (Flu)cloxacillin

No paediatric-specific data is available to inform the choice between β-lactams including cephalosporins and ASP for *S. aureus* bacteraemia and few children have been included in published trials evaluating these agents. Practice guidelines, however, often recommend ASP, such as oxacillin, nafcillin, or flucloxacillin, as first-line agents for the treatment of MSSA bacteraemia for both children and adults (10, 11). A number of recent meta-analyses, with data from retrospective and prospective cohort studies, have compared outcomes with cefazolin and ASP in adults with MSSA bacteraemia. These data demonstrate equivalence (12) or favour cefazolin over ASP (13, 14). Clinical trial evidence

is lacking to distinguish superiority between ASP and cefazolin for the treatment of MSSA bacteraemia in children and is an important aim in SNAP-PY to optimise treatment outcomes for children.

6.1.1.3. Vancomycin vs Vancomycin plus Cefazolin

Vancomycin is the first-line recommended treatment option for MRSA bacteraemia and has a long history of use in children, serving as a comparator to newer agents for treating *S. aureus* infections (15). However, clinical trial data supporting vancomycin use in children with *S. aureus* bacteraemia is limited (16, 17). A clinical trial in children aged 1 to 17 years with SAB (n=82) found treatment with vancomycin or cefazolin had comparable safety and efficacy to treatment with daptomycin, but was inadequately powered to assess noninferiority (16). Another RCT with 321 children aged ≤ 12 years with *S. aureus* skin and soft tissue infection, nosocomial pneumonia, catheter related bacteraemia or bacteraemia of unknown source, compared vancomycin with linezolid (17). Favourable outcomes were reported in both treatment groups; 74% versus 79% (P = 0.36), however, outcomes for the *S. aureus* bacteraemia subgroup were not reported (17). The limited clinical trial evidence available to guide the treatment of paediatric MRSA bacteraemia is reflected in the wide variation of practice by paediatrician's in a clinician survey (18). Most paediatricians preferred the use of combination antibiotics for directed MRSA bacteraemia therapy (22/38, 58%). Vancomycin-containing regimens (29/38, 76%) were preferred. With persisting MRSA-B and increasing case complexity in childhood, the number of different antibiotic combinations chosen increased from 8 to 19 in a recent clinician survey from ANZ (18). It is clear further comparator trials with vancomycin for MRSA bacteraemia are required to achieve consensus on best practice treatment approaches for children.

There is currently no RCT data in children or adults examining outcomes for vancomycin plus cefazolin versus vancomycin alone for MRSA bacteraemia. Laboratory and animal models examining the addition of a β-lactam to standard therapy for MRSA bacteraemia consistently demonstrate synergy (19). A retrospective study has also reported improved outcomes when β-lactams have been included during a treatment course for MRSA bacteraemia (19). The recent CAMERA2 (Combination Antibiotics for Methicillin Resistant *Staphylococcus aureus*) RCT included 352 adults with MRSA bacteraemia and demonstrated an increased risk of acute kidney injury (AKI) in the combination therapy group (beta-lactam with standard therapy), compared with standard therapy alone, resulting in no significant difference in the primary composite end point of mortality, bacteraemia, relapse, or treatment failure (35% vs 39%, respectively) (20). Cefazolin has been associated with a lower AKI rate than ASPs in retrospective data of adults with MSSA bacteraemia (21) and also when combined with vancomycin in the post hoc analysis from the CAMERA2 trial (20). In addition, children are at lower risk of vancomycin associated nephrotoxicity, likely due to less underlying comorbidities and therefore

outcomes may also differ from adult trial data (22, 23). Further assessment of the efficacy and safety of this combination in both children and adults are required through future RCT.

6.1.2. Adjunctive Treatment Domain

6.1.2.1. Clindamycin vs standard of care

In vitro studies have demonstrated that subinhibitory concentrations of clindamycin suppress *S. aureus* exotoxins, including a-toxins (a-haemolysin), TSST-1, Panton–Valentine leucocidin (PVL), b-haemolysin, d-haemolysin and enterotoxins, (24-27) and also down-regulate b-lactam-induced exotoxin production when given concurrently (28, 29). Clinical data on adjunctive clindamycin as antitoxin therapy in *S. aureus* infections is currently limited to case series and case reports (30, 31). A single double-blind placebo RCT has been published, which targeted a clinical syndrome (cellulitis), but not specifically *S. aureus* infection (32). This trial assessed 48 hrs of adjunctive clindamycin in addition to standard therapy (flucloxacillin) versus standard therapy alone in adults with cellulitis (32). Importantly patients with abscess were excluded, suggesting that *Streptococcus pyogenes* rather than *S. aureus* was the likely pathogen in most cases. Clinical improvement at day five was similar between combination and monotherapy groups (87% versus 81%, respectively, OR 1.55, 95% CI 0.81-3.01), with diarrhoea more common in clindamycin recipients (22% versus 9%, OR 2.7, 95%CI 1.41- 5.07) (32).

In a more recent prospective case series of children with MRSA pneumonia following influenza (N = 30, 87% previously healthy), for those who received vancomycin within the first 24 hours of hospitalisation, mortality was 12.5% (N = 2/16) for combination therapy with a second anti-MRSA antibiotic compared to 69.2% (N = 9/13) with vancomycin monotherapy (RR, 5.5; 95% CI, 1.4, 21.3; P = .003) (33). Significant limitations include small sample size, non-randomised design and despite reporting a mortality risk difference between duration from symptom onset to PICU admission; 4 days (interquartile range [IQR], 3.3, 4.8) for children who died vs 2 days (IQR, 2, 3) (p = .02) for those survived, this characteristic was not reported between treatment groups (33). Li et al. also retrospectively reviewed 92 cases of *S. aureus* necrotizing pneumonia (including 20 adolescents aged 14-18 years) and found that antibiotic therapy that included an antitoxin agent (clindamycin or linezolid) was associated with lower mortality (P 0.007) (31). Incomplete data, retrospective design and lack of severity-matched controls are limitations of this study. In another retrospective analysis of 269 adults with skin and skin-structure infections (146 culture positive: 70% MRSA, 15% MSSA), combination therapy with vancomycin and clindamycin was associated with a reduced hospital length of stay (LOS) compared with vancomycin alone in a subgroup (n=134) of patients with abscess (3.6

+1.5 versus 4.4 +2.3 days), OR –0.82 (95% CI –1.49 to – 0.15), P 0.016 (31). In addition, the 90-day readmission rate was lower in the combination group. Confounders, including age, diabetes, lack of vancomycin therapeutic monitoring data and a significantly higher proportion of those undergoing incision and drainage receiving combination therapy, limit the validity of the study. Conversely a retrospective case–control study examining 141 PVL-positive and 148 PVL-negative invasive *S. aureus* isolates from adults found 30-day mortality was not influenced by adjunctive linezolid or lincosamide therapy [2.7% (PVL positive) versus 5.3% (PVL negative), P 0.534] (34).

Despite a lack of high-quality evidence with no clinical trials performed, some antibiotic guidelines support consideration of clindamycin in conjunction with standard therapy for severe toxin-mediated *S. aureus* infections, including staphylococcal toxic shock syndrome and necrotizing fasciitis (15). British and French guidelines addressing the management of PVL-positive *S. aureus* infection recommend the addition of an antitoxin agent, e.g. clindamycin, linezolid and/or rifampicin, when toxin-mediated staphylococcal infection is confirmed or suspected (35). The in vitro evidence indicates that adjunctive clindamycin can reduce toxin production. The current clinical evidence to support adjunctive toxin suppression to improve clinical outcomes in *S. aureus* disease is weak and conflicting due to a lack of high-quality clinical data. Well-designed clinical studies, including RCTs, are needed to further define its therapeutic role.

6.1.3. Early Oral Switch Domain

Minimal evidence exists to guide duration of IV therapy for children with SAB. Historically, treatment in children has been extrapolated from adult data. There has been only one RCT providing information on duration and outcomes, involving 120 neonates with all-cause bacteraemia (36). On subgroup analysis of neonates with SAB, 4 of 7 (57%) with 7-day therapy failed treatment compared with 14-days of therapy, (0 of 7 [0%] (P = .022) (36). Neonates are a high-risk group and extrapolating these data to older children is challenging. For children with SAB without focus, an IV duration of 7-14 days is currently recommended, although earlier transition to oral antibiotics may be possible in those with skeletal infections who have adequate source control and good clinical response (37). In an observational study of 192 children with skeletal infections, of the 35 with MRSA-B those who received <7 days of vancomycin and appropriate oral antibiotic stepdown did not have increased relapse compared to those receiving ≥7 days of vancomycin (38).

For SAB with endocarditis, 4-6 weeks is recommended for children (10, 37). In a recent prospective RCT, the POET study, researchers examined partial oral versus IV antibiotic treatment for left-sided endocarditis for 87 adult patients with MSSA endocarditis (unknown number with SAB) (39). Changing to oral antibiotic treatment after a minimum of 10 days of IV treatment was non-inferior to continued IV antibiotic therapy for the primary composite outcome of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia (including for *S. aureus* endocarditis, odds ratio 0.84 [95% CI 0.15-4.78]) (39). This study did not, however, include children or those with MRSA.

6.1.4. PET/CT Domain

PET/CT is broadly used as an imaging modality and is generally considered well-tolerated. There are rare and mild adverse effects from contrast agents such as nausea, headache, skin reaction, and very rarely anaphylaxis. PET/CT does result in low level radiation exposure, and therefore needs to be clinically justified as would be the case in a patient with SAB. It would not be offered to pregnant participants or children less than 18 years of age routinely due to the radiation risks on the developing foetus and child, hence their exclusion from this domain. Participants who are breastfeeding are also excluded, due to the potential radiation/nuclear medicine risks via breastfeeding. Children less than 18 years of age are additionally excluded from this domain, as PET/CT requires the patient to lie still for an extended period and may require sedation in younger patients. Other imaging modalities in SNAP will be considered for children, adolescents, and pregnant participants if these are included in the trial in the future based on a similar risk/benefit assessment.

7. TRIAL DESIGN

7.1. *Paediatric-specific eligibility criteria*

The eligibility criteria for platform entry are outlined in the Core Protocol Section 6.5, where there is no age-based exclusion criterion. Specific safety considerations and outcome data relevant to this appendix are for paediatric patients enrolled in SNAP.

This section of the protocol highlights specific differences in eligibility criteria for the core protocol and for domain specific appendices.

The eligibility criteria for platform entry in the Core Protocol Section 6.5 directly apply to children.

Antibiotic backbone domain for PSSA/MSSA silo eligibility criteria in the PSSA/MSSA DSA (Section 8.2) directly apply to children.

Antibiotic backbone domain for MRSA silo eligibility criteria in the MRSA DSA (Section 8.2) directly apply to children.

Adjunctive antibiotic domain eligibility criteria in the adjunctive antibiotic DSA (Section 8.2) directly apply to children.

Early oral switch domain eligibility criteria differ at point 8.2.1 to allow the inclusion of children with uncomplicated native bone and joint infections. Other eligibility criteria at day 7 and day 14 remain unchanged.

Specifically (amendment in italics):

Primary focus is either line related (either central or peripheral IV cannula), skin and soft tissue, or *uncomplicated bone and joint infection* AND source control achieved (for 'line-related' this means line removed; for 'skin and soft tissue' means site PI considers source control to have been achieved and any abscess more than 2cm diameter has been drained, *and for uncomplicated, native bone and joint infection either surgical drainage has occurred or the clinician deems this is not necessary*).

PET/CT domain eligibility criteria will not be relevant to children and adolescents; <18 years of age is an exclusion criteria for this domain.

7.2. *Endpoints*

7.2.1. Primary endpoint

The primary endpoint for this appendix is the platform primary endpoint (all-cause mortality at 90 days after platform entry) as specified in Core Protocol Section 6.8.

7.2.2.Secondary endpoints

7.2.2.1. Core secondary endpoints

All secondary core platform endpoints as specified in the Core Protocol Section 6.8 remain applicable, with minimal modifications to the following:

1. Health economic costs as detailed in the cost utility analysis appendix with the following amendments for children:

   At 90 days this will be measured in children by:

   1.1. If the primary caregiver has been working in paid employment, number of days of work missed by the primary caregiver due to caring for their child while the child was unwell with a bloodstream infection?

   1.2. If the secondary caregiver has been working in paid employment, number of days of work missed by the secondary caregiver due to caring for their child while the child was unwell with a bloodstream infection?

   1.3. If attending childhood education or school, how many days of early childhood education or school did the child miss due to being unwell with a bloodstream infection?

2. Proportion of participants who have returned to their usual level of function at day 90 (this replaces the modified Functional Bloodstream Infection Score)

   2.1. Has your child returned to their usual level of activity?

3. Desirability of outcome ranking 1 (modified Antibiotic Resistance Leadership Group version) with item 2.1 above as the paediatric tie breaker

4. Desirability of outcome ranking 2 (SNAP version) with item 2.1 above as the paediatric specific measure of 'return to usual level of function by day 90'

7.2.2.2. Paediatric-specific secondary endpoints

The paediatric composite endpoint will comprise of four existing secondary SNAP endpoints that have already been shown in the ISAIAH study (1) to be useful outcome measures. The chosen endpoints focus on either mortality, markers of relapse, or extended hospitalisation as follows:

1. Mortality by day 90 following platform entry
2. Microbiological treatment failure defined as positive sterile site culture for *S. aureus* (of the same silo as the index isolate) between 14 and 90 days after platform entry
3. Diagnosis of new foci between 14 and 90 days after platform entry
4. Length of total index hospitalisation of >30 days from the time of platform entry. Total index hospitalisation is defined as a continuous admission to any healthcare facility, including rehabilitation hospitals, and hospital-in-the-home or outpatient parenteral antimicrobial therapy services.

If an event is observed in any of the four endpoints, then the composite endpoint will be considered to have been met.

7.2.3. Rationale for these paediatric-specific outcomes

Mortality for children with SAB is far lower than adults. Whilst the most robust, meaningful and practice changing endpoint for this trial (which integrates children and adults into the same clinical trial) is mortality at 90 days, there needs to be an additional secondary outcome that will support clinical care.

A paediatric composite endpoint that includes four of the secondary outcomes collected across the SNAP trial, will be compiled. This composite endpoint at 90 days will include already collected data including 90-day all-cause mortality, markers of disease relapse (microbiological treatment failure, diagnosis of new foci), and a summative duration of hospitalisation which is more than twice the median duration of hospitalisation (length of stay beyond 30 days from the time of platform entry). In the ISAIAH cohort of 552 children, a composite summary of all-cause mortality, ICU admission, relapse and hospitalisation > 30 days was a useful measure of disease severity (1). We have modified it to align with already collected secondary endpoints across the SNAP trial.

8. TRIAL CONDUCT

8.1. *Paediatric-specific data collection*

8.1.1. Paediatric-specific study timeline

All core study visit details are specified in the Core Protocol (Section 8.8) and Domain-specific appendices.

The weight of a child < 18 years needs to be recorded at baseline for weight-based antibiotic prescribing.

Whilst an echocardiogram is recommended in an adult patient with SAB, it is not routinely performed in children with SAB. When performed, a transthoracic echocardiogram is usually performed in children due to lower subcutaneous fat allowing for good cardiac windows achieved through the thorax.

If a blood culture drawn on any day after the day of the index blood culture is negative (i.e., reports no growth after 48 hours of incubation), then a platform day 2 blood culture is not needed in those aged <18 years.

8.2. *Domain specific considerations*

For each domain, the existing safety and dosing data for each drug in children will be considered by the Paediatric Working Group and Trial Steering Committee.

8.2.1. Drug dosing and safety for domain specific therapeutics offered to children

8.2.1.1. Antibiotic Backbone Domain

PSSA Treatment interventions

Standard dose

Those randomised to (flu)cloxacillin, and flucloxacillin is available:

- (Flu)cloxacillin 50mg/kg/dose up to 2 g max dose every 6 hours intravenously

Those randomised to (flu)cloxacillin, and cloxacillin but not flucloxacillin is available:

- Cloxacillin 50mg/kg/dose up to 2 g max dose every 4 hours intravenously

Those randomised to penicillin can use one of two dosing regimens, at the treating clinicians' discretion:

- Benzylpenicillin (=Penicillin G) 50mg/kg/dose up to 1.8g max dose (=3 million units) every 4 hours intravenously (preferred option)
  OR
- Benzylpenicillin (=Penicillin G) 60mg/kg/dose up to 2.4g max dose (=4 million units) every 6 hours intravenously

For patients with critical illness (defined as being admitted to ICU or having septic shock), endocarditis or central nervous system infection (includes brain or spinal cord infection, subdural empyema or CNS device-related infection, but does not include epidural abscess):

- (Flu)cloxacillin 50mg/kg/dose up to 2 g max dose every 4 hours intravenously

OR

- Benzylpenicillin (=Penicillin G) 60mg/kg/dose up to 2.4 g max dose (=4 million units) every 4 hours intravenously

Dosing adjustment for renal impairment:

(Flu)cloxacillin:

eGFR ≥10mL/minute: normal dosing

eGFR <10mL/minute: 50% of the standard dose 6 to 8 hourly (40)

Cloxacillin:

No dose adjustment necessary (41)

Benzylpenicillin:

eGFR ≥50mL/minute: normal dosing

eGFR ≥10 to <50mL/minute: 100% of the standard dose every 8 to 12 hours

eGFR <10mL/minute: 100% of the standard dose every 12 hours (42)

MSSA Treatment interventions

Standard dose

Those randomised to (flu)cloxacillin, and flucloxacillin is available:

- (Flu)cloxacillin 50mg/kg/dose up to 2g max dose every 6 hours intravenously

Those randomised to (flu)cloxacillin, and cloxacillin but not flucloxacillin is available:

- Cloxacillin 50mg/kg/dose up to 2g max dose every 4 hours intravenously

Those randomised to cefazolin:

- Cefazolin 50mg/kg/dose up to 2g max dose every 8 hours intravenously

For patients with critical illness (defined as being admitted to ICU or having septic shock), endocarditis or central nervous system infection (includes brain or spinal cord infection, subdural empyema or CNS device-related infection, but does not include epidural abscess):

- (Flu)cloxacillin 50mg/kg/dose up to 2g max dose every 4 hours intravenously

OR

- Cefazolin 50mg/kg/dose up to 2g max dose every 6 hours intravenously

Dosing adjustment for renal impairment:

(Flu)cloxacillin:

eGFR ≥10mL/minute: normal dosing

eGFR <10mL/minute: 50% of the standard dose 6 to 8 hourly (40)

Cloxacillin:

No dose adjustment necessary (41)

Cefazolin – give an initial loading dose of the standard mg/kg dose then:

eGFR ≥40 to <70mL/minute: 60% of the total daily dose given in 2 divided doses, 12 hours apart

eGFR ≥20 to <40mL/minute: 25% of the total daily dose given in 2 divided doses, 12 hours apart

eGFR <20mL/minute: 10% of the total daily dose given once daily (43)

MRSA Treatment Interventions

The choice of vancomycin or daptomycin will be at the clinician's discretion as per local practice.

Vancomycin

a) Standard vancomycin dosing in normal renal function:

- The initial starting dose of Vancomycin is 15mg/kg/dose up to 500mg max every 6 hours or 30mg/kg/dose up to 1g max every 12 hours intravenously, except for neonates where dosing will depend on gestational age as per the below table
- For neonates <1 month of age there are variety of available dosing regimens by postmenstrual age and postnatal age that do not have a strong evidence base that one is superior to another. Please use local guidelines for vancomycin dosing. If there are no local guidelines available, the below table has been provided for vancomycin dosing to guide clinicians in this circumstance.

Postmenstrual age (PMA)	Postnatal age	Dose
≤29 weeks	0 to 14 days	10 to 15mg/kg/dose every 18 hours
	≥14 days	10 to 15mg/kg/dose every 12 hours
≥30 weeks to ≤36 weeks	0 to 14 days	10 to 15mg/kg/dose every 12 hours
	≥14 days	10 to 15mg/kg/dose every 8 hours
≥37 weeks to ≤44 weeks	0 to 7 days	10 to 15mg/kg/dose every 12 hours
	≥7 days	10 to 15mg/kg/dose every 8 hours
≥45 weeks	ALL	10 to 15mg/kg/dose every 6 hours

b) **Dosing adjustment of vancomycin for renal impairment:**

Dose adjustment in renal impairment should be conducted in combination with regular therapeutic drug monitoring. Suggested starting intervals:

eGFR 70-89mL/minute: 100% of the standard dose given 8 hourly

eGFR 30-69mL/minute: 100% of the standard dose given 12 hourly

eGFR 15-29mL/minute: 100% of the standard dose given 24 hourly

eGFR < 15mL/minute: 100% as a single dose with subsequent doses based on therapeutic drug monitoring (44).

Sites may follow local guidelines for the use of vancomycin. In general, it would be expected that dosing follows similar principles as those in the Australian Therapeutic Guidelines: Antibiotic and the consensus guidelines from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Paediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists (45).

Daptomycin

a) Standard daptomycin dosing in normal renal function:

Children < 1 years	Daptomycin not usually recommended due to the musculoskeletal, neuromuscular and nervous system effects seen in canine models
Children 1 to <7 years	12mg/kg/dose IV given 24-hourly
Children ≥7 to<12 years	9 mg/kg/dose IV given 24-hourly
Adolescents ≥12 to <18 years	7 mg/kg/dose IV given 24-hourly

b) Daptomycin dosing in renal impairment:

There is limited information about dose adjustment for Daptomycin in paediatric patients with impaired renal function. Use the above table and modify the dose according to the patient's eGFR

eGFR	**Recommended dose**
≥ 30mL/minute:	normal dose
≥10 to <30mL/minute	67% of the normal dose 24 hourly
<10mL/minute	67% of the normal dose 48 hourly.
Intermittent haemodialysis	67% of the normal dose 48 hourly after dialysis
Peritoneal dialysis	67% of the normal dose 48 hourly
Continuous renal replacement therapy	8mg/kg/dose given every 48 hours.

Cefazolin

a) Cefazolin dosing in normal renal function:

- Cefazolin 50mg/kg/dose up to 2g max dose every 8 hours intravenously

b) Dosing adjustment for cefazolin with renal impairment:

- Cefazolin – give an initial loading dose of the standard mg/kg dose then:

eGFR ≥40 to <70mL/minute: 60% of the total daily dose given in 2 divided doses, 12 hours apart

eGFR ≥20 to <40mL/minute: 25% of the total daily dose given in 2 divided doses, 12 hours apart

eGFR <20mL/minute: 10% of the total daily dose given once daily (43)

8.2.1.2. Adjunctive Treatment Domain

Clindamycin (or lincomycin where clindamycin is not available. Note – lincomycin is only available as an IV preparation):

a) Standard dosing for normal renal function:

- IV clindamycin: 15mg/kg/dose for children max 600mg/dose q8h for 5 days OR
- PO clindamycin: 10mg/kg/dose for children, max 450mg/dose q8h for 5 days.

b) Dosing adjustment for renal impairment:

Clindamycin:

No dose adjustment necessary (40)

Lincomycin:

eGFR ≥50mL/minute: normal dosing

eGFR ≥10 to <50mL/minute: 100% of the standard dose every 8 to 12 hours

eGFR <10mL/minute: 100% of the standard dose every 12 to 24 hours (40)

8.2.1.3. Early Oral Switch Domain

EOS Treatment Interventions

Please see table 1 and 2.

Table 1. Hierarchy of recommended oral antibiotics for early oral switch by silo (i.e. susceptibility of *S. aureus*).

Site PIs and treating clinicians are encouraged, but not mandated, to select the highest antibiotic on this list which is appropriate for a given patient.

Silo	Recommended oral antibiotic according to allocated backbone domain	
PSSA	**Benzylpenicillin**	**(Flu)cloxacillin**
	1. Amoxicillin	1. Cefalexin/cefadroxil
	2. Cefalexin/cefadroxil	2. Flucloxacillin/dicloxacillin
	3. Flucloxacillin/dicloxacillin	3. Amoxicillin
	4. Linezolid	4. Linezolid
MSSA	**(Flu)cloxacillin**	**Cefazolin**
	1. Cefalexin/cefadroxil	1. Cefalexin/cefadroxil
	2. Flucloxacillin/dicloxacillin	2. Flucloxacillin/dicloxacillin
	3. Linezolid	3. Linezolid
MRSA	**Vancomycin/daptomycin**	**Vancomycin/daptomycin + cefazolin**
	1. TMP-SMX	1. TMP-SMX
	2. Linezolid	2. Linezolid
	3. Fluoroquinolone + rifampicin	3. Fluoroquinolone + rifampicin
	4. Fusidic acid + rifampicin	4. Fusidic acid + rifampicin

Table 2. Antibiotic options for early oral switch in SAB – dosing, administration, pharmacological properties

Principles:

- For beta-lactams, maximum doses have been recommended to overcome theoretical issues with drug exposure (bioavailability). Lower doses in specific circumstances have been recommended in the footnotes.
- Dosing regimens to minimise patient inconvenience have been prioritised, as explained in footnotes.
- Doses are suggestions only and alternate doses used as standard local practice can be maintained.
- Contraindications, including significant drug interactions, are not listed and are the responsibility of the prescribing team to review and manage. Some considerations are provided to aid the choice of drug.
- We have not recommended dose changes for obesity or pregnancy in the setting of early oral switch (i.e. step-down therapy after a period of intravenous therapy/source control/clinical stability). Despite a potential effect of obesity and pregnancy on pharmacokinetics (increased volume of distribution), we will not proceed to dose adjustment for step-down therapy.
- With increased creatinine clearance in pregnancy, there is a theoretical concern that the concentration of the antibiotics may not be over the required MIC for a sufficient period of time. However, general practice in obstetric dosing of antibiotics is to dose at the highest end of the dosing range, as is currently planned in the SNAP study.

Drug	**Standard Adult Dose**	**Dose in renal impairment[1,2]**	**Paediatrics** **(Over 1 month)**	**Neonates (<30 days)**
Amoxicillin	1g PO 6-hourly [3,4]	CrCl 10 to 30mL/min20mg/kg/dose 12 hourly	25mg/kg/dose PO (maximum 2 g) TDS (48)	<7 days: 50mg/kg/dose PO 12 hourly

[1] Dose derived from Australian Therapeutic Guidelines: Antibiotic v16, 2019, Sandford Guide and Licensed Product Information from FDA.

[2] HD: haemodialysis, PD: peritoneal dialysis.

[3] Dose derived from POET trial (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) (46)

[4] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with amoxicillin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

		CrCl less than 10mL/min, HD and PD: 20mg/kg/dose 24-hourly (47)		≥7 days: 50mg/kg/dose 8 PO hourly (48)
Cefadroxil	1g PO 12-hourly	CrCL 10 to 29mL/minute and HD: 15mg/kg/dose every 24 hours CrCl <10mL/minute and PD: 15mg/kg/dose every 36 hours (49)	Not very available for paeds 15mg/kg/dose PO (maximum 1g dose) BD	
Cefalexin	1g PO 6-hourly[5,6]	CrCl 30-50mL/minute: 10mg/kg/dose (maximum 500mg) 8 hourly CrCl 10-29mL/minute: 10mg/kg/dose (maximum 500mg) 12 hourly CrCl <10mL/minute, HD or PD: 10mg/kg/dose (maximum 500mg) 24 hourly (51)	25mg/kg/dose PO QID (max dose 1g QID) OR 45mg/kg/dose PO TDS (max dose 1.5g TDS) NB TDS dosing is only for children > 12 months of age.	<7 days: 25mg/kg/dose PO BD ≥7 to 20 days: 25mg/kg/dose PO TDS ≥21 days: 25mg/kg/dose PO QID (52)
Ciprofloxacin PLUS rifampicin (use only in combination)	**Ciprofloxacin**750mg PO 12-hourly	CrCl 10-29mL/minute: 10-15mg/kg/dose 18 hourly CrCl <10mL/minute, HD or PD: 10-15mg/kg/dose 24 hourly CRRT: 10-15mg/kg/dose 12 hourly (53)	20mg/kg/dose PO (maximum 750mg) BD (48)	10mg/kg/dose PO BD (52)

[5] Clinical efficacy in uncomplicated SAB has been demonstrated at a dose of 1g orally q8h (50)

[6] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with cefalexin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

	Rifampicin: Weight <60kg: 600 mg PO per day; weight >60kg: 900mg PO per day.[7, 8,9]	No change to standard dose.	20mg/kg/dose PO (maximum 600mg) daily (48)	5-10mg/kg/dose PO BD (52)
Clindamycin	450mg PO 8-hourly[10]	No change to standard dose	10mg/kg/dose PO (maximum 450mg) TDS	Avoid using in neonates where an alternative is available
Cloxacillin	1g PO 6-hourly[11]	No change to standard dose.	50mg/kg/dose PO (maximum 500mg) QID	Nil info found hence avoid in neonates
Dicloxacillin	1g PO 6-hourly[12,13]	CrCl less than 10mL/min, HD or PD: 100% q8h. CRRT: standard dose.	25mg/kg/dose PO (maximum 1000mg) QID (48)	Nil info found hence avoid in neonates
Doxycycline	100mg PO 12-hourly	No change to standard dose.	1-2mg/kg/dose BD PO (maximum 200mg per day) (56)	Nil info found hence avoid in neonates

[7] Doses above 600 mg per day should be divided into two doses.

[8] Use with caution in liver disease - can cause hepatotoxicity.

[9] Dose derived from the ARREST trial (54)

[10] For oral administration 450mg is the maximum dose licensed by the TGA. Clindamycin dosed 8-hourly showed significantly longer bactericidal activity against *S. aureus* when compared to 12-hourly regimens, (87.5 to 100% versus 49.6 to 77.1%, P < 0.001) (55)

[11] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with cloxacillin 1g q6h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

[12] Dose derived from POET trial (46)

[13] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with dicloxacillin 1g q6h or 1g q8h at the discretion of the treating clinician. We recommend giving probenecid with food to prevent nausea.

Flucloxacillin	1g PO 6-hourly[14,15]	CrCl less than 10mL/min, HD or PD: 100% q8h. CRRT: standard dose. (40, 52)	25mg/kg/dose (maximum 1g) PO QID	<7 days: 25mg/kg/dose BD ≥7 to 20 days: 25mg/kg/dose TDS ≥21 days: 25mg/kg/dose QID (52)
Fusidic acid PLUS rifampicin (use in combination only)	**Fusidic acid:** 500mg PO 8- to 12-hourly	No change to standard dose.	**Oral doses of sodium fusidate (tablets):** 12mg/kg PO (to a maximum of 500mg) TDS. **Oral doses of fusidic acid (liquid):** Children 1 month to 18 years: 15mg/kg PO (to a maximum of 750mg) TDS	15mg/kg/dose TDS Using the oral suspension (52)
	Rifampicin: Weight <60kg: 600 mg PO per day; weight >60kg: 900mg PO per day.[16, 17]	No change to standard dose.	20mg/kg/dose (maximum 600mg) daily. (48)	5-10mg/kg/dose BD (52)

[14] Clinical efficacy in uncomplicated SAB has been demonstrated at a dose of 1g orally q8h (50)

[15] Probenecid (dose: 500mg if CrCl 60 mL/min or more, 250mg if CrCl between 60 to 30 mL/min, do not use if CrCL less than 30 mL/min) may be co-administered with each dose of beta-lactam to improve drug exposure. Administer with flucloxacillin 1g q6h or 1g q8h at the discretion of the treating clinician (57). We recommend giving probenecid with food to prevent nausea.

[16] Doses above 600 mg per day should be divided into two doses.

[17] Use with caution in liver disease - can cause hepatotoxicity.

Levofloxacin PLUS rifampicin (use in combination only)	**Levofloxacin:** 750mg PO daily	CrCl 10-29mL/minute: 5 to 10mg/kg/dose 24 hourly CrCl <10mL/minute, HD or PD: 5 to 10mg/kg/dose 48 hourly CRRT: 10mg/kg/dose 24 hourly (58)	10-20mg/kg/DAY PO (maximum 500mg per DAY) in one or 2 divided doses (59)	Nil information found hence avoid in neonates
	Rifampicin: Weight <60kg: 600 mg PO per day; weight >60kg: 900mg per day.[18, 19]	No change to standard dose.	20mg/kg/dose PO (maximum 600mg) daily. (48)	5-10mg/kg/dose BD (52)
Linezolid	600mg PO 12-hourly[20, 21]	No change to standard dose. Metabolites may accumulate if eGF <30mL/minute (52, 62)	<12 years: 10mg/kg/dose PO (maximum 600mg) TDS >12 years: 600mg PO BD (48)	<7 days: 10mg/kg BD ≥7 days: 10mg/kg/dose TDS (52)
Moxifloxacin PLUS rifampicin (use in combination only)[22]	**Moxifloxacin:** 400mg PO daily	No change to standard dose.	10mg/kg/dose PO once daily (59)	Nil information found hence avoid in neonates
	Rifampicin: Weight <60kg: 600 mg PO	No change to standard dose.	20mg/kg/dose PO (maximum 600mg) daily.	5-10mg/kg/dose BD (52)

[18] Doses above 600 mg per day should be divided into two doses.

[19] Use with caution in liver disease - can cause hepatotoxicity.

[20] Risk of haematological toxicity increases with use beyond 14 days (60)

[21] Pyridoxine 50mg-100mg/day to prevent or delay anaemia can be considered if using linezolid for > 7 days; evidence for benefit conflicting (61)

[22] Rifampicin may reduce serum concentrations of moxifloxacin, though the clinical significance of this interaction remains uncertain. Consider using another quinolone in combination with rifampicin

	per day; weight >60kg: 900mg PO per day.[23, 24]		(48)	
Tedizolid	200mg once daily	No change to standard dose.	Children ≥12 years: 200mg once daily	Nil information found hence avoid in neonates
Trimethoprim plus sulfamethoxazole (TMP+SMX)	320/1600 mg PO 12-hourly or 160/800 mg PO 8-hourly	CrCl 26-50mL/min: normal for 14 days, then 160/800mg 12-hourly. CrCl 15 to 25mL/min: normal for 3 days, then 320/1600mg 24-hourly. For CrCl less than 15mL/min: avoid use.[25]	5mg/kg/dose PO (max 160mg TMP component) TDS PLUS: folic acid 0.5mg/kg/dose (maximum 5mg) once daily whilst on high dose	Not generally used in neonates hence avoid in neonates

[23] Doses above 600 mg per day should be divided into two doses.

[24] Use with caution in liver disease - can cause hepatotoxicity.

[25] Sulfamethoxazole can cause pancreatic insulin release, resulting in clinically significant hypoglycaemia, particularly in patients with renal impairment, receiving high doses, or concomitantly taking a sulfonylurea (63)

9. STATISTICAL CONSIDERATIONS

9.1. *Estimands, endpoints, and intercurrent events*

9.1.1. Primary estimand

The primary estimand, endpoint, and intercurrent events strategy for this domain is the core SNAP primary endpoint (i.e. all-cause mortality 90 days after platform entry) and a treatment policy strategy, as specified in Statistical Analysis Appendix (Section 6.1).

9.1.2. Secondary estimands

All core secondary estimands, endpoints, and intercurrent events strategies are specified in the Statistical Analysis Appendix (Section 6.2). Domain-specific endpoints are specified in the respective domain-specific appendices (Sections 8.5).

Estimand/Objective/Target population	**Endpoint/Population-level summaries**	**Intercurrent events strategy**
Estimand 14.P 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 90 days after platform entry, in platform eligible paediatric participants.	Endpoint: Return to usual level of function 90 days after platform entry #. Usual level of function is defined, for the paediatric population, as parent/guardian confirmation that the child has returned to their usual level of activity. 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 15.P 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 platform eligible paediatric participants.	Endpoint: DOOR1 score at platform Day 90. For the paediatric population, estimand 14.P will be the tie breaker. 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 each relevant cell.	Treatment policy strategy (intent-to-treat principle)
Estimand 16.P 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 platform eligible paediatric participants.	Endpoint: DOOR2 score at platform Day 90. For the paediatric population, estimands 14.P will be the measure of 'return to usual level of function by day 90'. Population summary: As for estimand 15.P.	Treatment policy strategy (intent-to-treat principle)

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

The single paediatric-specific secondary estimands is defined as follows:

Estimand/Objective/Target population	**Endpoint/Population-level summaries**	**Intercurrent events strategy**

Estimand P.1 To evaluate, within each relevant cell, the effect of revealed randomised interventions compared to domain control on the probability of any of the four events defined by the composite endpoint occurring, in platform eligible paediatric participants.	Endpoint: If an event is observed in any of the four endpoints described in Section 7.2.2.2, then the composite endpoint will indicate that there has been an event. Population summary: As for estimand 14.P.	Treatment policy strategy (intent-to-treat principle)

9.2. *Statistical modelling*

9.2.1. Primary model

The population summary (log-odds ratio) for the binary primary endpoint (all-cause mortality at 90 days) will be modelled using a Bayesian binomial model with a logit link. See the Statistical Analysis Appendix (Section 7.1).

9.2.2. Secondary models

The population summaries for all core secondary endpoints as specified in the Core Protocol (Section 6.8.2) will be modelled as specified in the Statistical Analysis Appendix (Section 7.3), with the minor modifications to estimands 14.P, 15.P, and 16.P. The population summaries for all domain-specific secondary endpoints as specified in the respective domain-specific appendices (Sections 10.1.2) will be modelled as specified in the Statistical Analysis Appendix (Section 10.2). Note that where the endpoints specified in the either the core or domain-specific appendices have been modified for the paediatric population (as in 7.2.2.1), they will be analysed for the paediatric population only.

The paediatric-specific endpoint P.1 described in Section 7.2.2.2 is binary and has a log-odds population summaries that will be modelled using a Bayesian binomial model with a logit link. See the Statistical Analysis Appendix.

9.3. *Decision criteria*

Decision criteria for trial adaptations will be based on results obtained for the adult population only and according to what is stated in the domain-specific appendices (Sections 10.3) and as detailed in the Statistical Appendix.

9.4. *Randomisation*

Paediatric participants will be randomised as a separate stratum into each domain according to the strategies outlined in the respective domain-specific appendices (Sections 10.4).

9.5. *Pre-specified secondary analyses*

Any pre-specified secondary analyses will be performed according to the strategies outlined in the respective domain-specific appendices (Sections 10.6) and as detailed in the Statistical Appendix.

10. ETHICAL CONSIDERATIONS

10.1. *Paediatric-specific consent issues*

In addition to the procedures for obtaining informed consent outlined in the Core Protocol section 8.4, additional age-appropriate information sheets will be provided to children and adolescents and their families to provide further information about SNAP-PY.

Parents and caregivers will be approached to provide informed consent. Children > 12 years will have their assent to participate in the trial documented.

10.2. *Adverse neonatal, infant, child or adolescent screening results*

All interventions being trialled are standard of care. As such there are no additional follow up visits beyond day 90 other than those arranged as part of routine clinical care by the treating team.

11. GOVERNANCE ISSUES

11.1. *Funding of paediatric-specific appendix*

Funding sources for SNAP are specified in the Core Protocol. The following additional grants have been secured for SNAP-PY:

New Zealand:

Webb R, Best E, Voss L, Walls G, Bowen A, Morpeth S, Campbell A. SNAP-PY: Staphylococcus aureus Network Adaptive Platform trial: Paediatrics and Youth. Athlae Lyon Starship Research Award, Starship Foundation 2020 (A$195,767)

11.2. *Appendix-specific declarations of interest*

All investigators involved in SNAP maintain a registry of interests on the SNAP website. These are updated periodically and publicly accessible on the study website.

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13.APPENDIX 1

Summary of children (n=292) with *Staphylococcus aureus* bacteraemia randomly assigned into clinical trials

Author Year Country	N* (total=292)	Clinical trial question	Primary(1) and secondary (2) outcomes	Clinical efficacy findings	Safety findings
Arriete (16) 2018 USA	82/82	Randomised evaluator blinded, multicentre phase 4 trial IV daptomycin versus SOC (primarily vancomycin or cefazolin) for SAB	1) Evaluate daptomycin safety in children receiving ≥1 dose 2) Comparing daptomycin efficacy with SOC: trial not powered to assess non-inferiority	Clinical success (measured by complete/partial resolution of bacteraemia signs and symptoms 7-14 days after end of treatment) rates were similar for daptomycin (88%) and SOC (77%; 95%CI for difference -9%-31%)	15% of patients had drug-related adverse events (diarrhoea: 4% daptomycin, 8% SOC, raised CK: 4% daptomycin, 0% SOC)
Peltola (64)	130/265	Prospective, quasi-randomised trial comparing	1) Full recovery was defined as the patient free of symptoms/signs	All patients recovered with an approximately 3-week (mostly oral) course of clindamycin or first-	Loose stools were reported slightly less frequently in the

2012 Finland		clindamycin with first generation cephalosporins in children with acute osteoarticular infections aged 3 months to 15 years. IV therapy was given for the first 2-4 days then oral therapy with the same equivalent agent was continued	of OA infection with no antimicrobials being readministered for this indication after the treatment course during the 12-month follow-up 2) Time to normalisation of laboratory indices between the clindamycin and cephalosporin recipients and hospital LOS	generation cephalosporin. No treatment failures in both groups. No MRSA in this cohort and limited surgical interventions, question the generalisability of these results.	clindamycin group than in the cephalosporin group (1%, 95% CI 0-4) vs 7%, 95% CI 4-14) respectively. Two clindamycin recipients developed a rash.
Chowdhary(36) 2006 India	14/120	Neonates ≥32wk ≥1500gm with blood culture proven sepsis without meningitis or deep-seated foci and clinically remitted by day 5 were	1) Treatment failure within 28 days defined as positive blood culture, clinical signs, CRP >12m/l or expert opinion	Out of the 14 neonates with SAB, in the 7-day group, 4/14 (28.6%) had treatment failure, whereas in the 14-day group all had successful treatment (P=0.02). 39 patients were excluded prior to randomisation because they were	No subjects developed deranged LFT, EUC or skin rash in either group.

		randomised to either 7-days or 14-days of IV antibiotic therapy	2) Common adverse effects related to antibiotic usage evaluated on the 7th and 14th day including skin rashes, deranged LFT/EUC	still symptomatic on days 6 and 7 of antibiotic therapy. *S. aureus* constituted 61.5% of culture isolates of neonates who were still symptomatic on day 6 and 7 (p=0.0001)	
Kaplan(17) 2003 USA	66/321 with *S. aureus* infection (unknown number with SAB)	Children with gram positive infections were randomised 2:1 to receive IV linezolid or vancomycin followed by an appropriate oral agent for total duration of 10-28 days	1) Clinical efficacy was assessed by evaluating clinical outcome. Cure: defined as a resolution of the baseline clinical signs and symptoms of infection by day 5 and after 15 doses of treatment. Failure was defined as the persistence of signs and symptoms of infection	Clinical cure rates were 79% linezolid, 74% vancomycin (p=0.36). Pathogen eradication rates in microbiological evaluable patients were high for linezolid 94% versus vancomycin 95% (p=0.82).	Significantly fewer linezolid treated patients had drug-related adverse events compared with vancomycin (19% vs 34% respectively p= 0.003). Hematological events were uncommon and similar between treatment groups.

			after 2 days and 6 doses of treatment		

Abbreviations: *N - number of children aged ≤18 yrs. with *S. aureus* bacteraemia enrolled in the clinical trial; SOC - standard of care; LOS – length of stay; OA – osteoarticular; SAB - *S. aureus* bacteraemia; MRSA – methicillin resistant *S. aureus*; CI – confidence interval; LFT - liver function test; EUC - electrolytes urea creatinine; CRP - C-reactive protein; p – p value.