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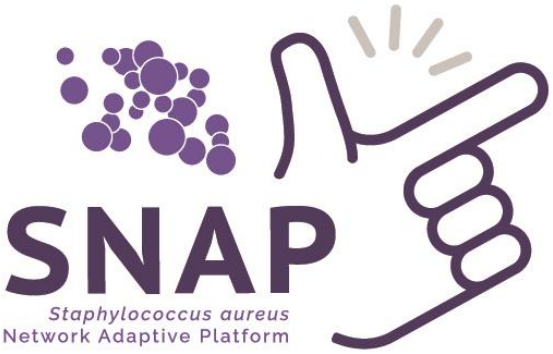


Appendix to Core Protocol:

SNAP-R Registry Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

SNAP-R Registry Appendix Version 2.0 dated 24 March 2023

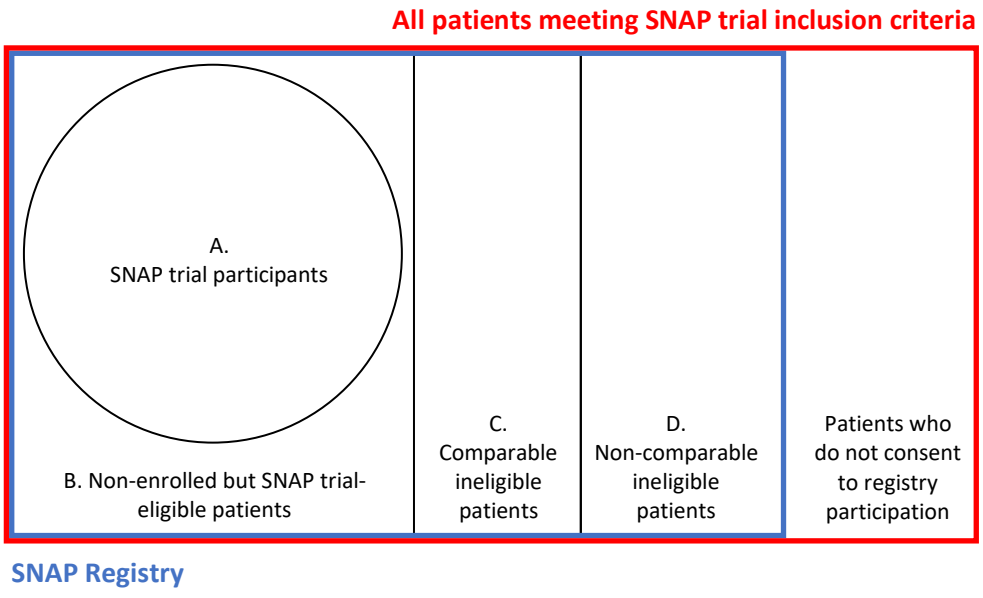
Summary

The registry associated with the *Staphylococcus aureus* bacteremia Network Adaptive Platform (SNAP) trial is a clinical quality registry intended to encourage best practice in the care of patients with *S. aureus* bacteremia (SAB) outside the randomised interventions of the trial. Registry data will also be used to place the randomised cohort in the context of the broader population of patients with SAB to assess the representativeness of the enrolled cohort.

The SNAP registry (SNAP-R) will use an opt-in consent approach to allow collection of a restricted subset of the data collected in the trial. These data will include demographics, prognostic data, quality-of-care indicators, and outcome data, and will be collected at registry entry, hospital discharge and day 90 vital status retrospectively via linkage. These data will be combined with those collected for trial participants to create the dataset for registry analyses.

Figure 1 presents the sub-cohorts contained in SNAP-R. Participation into the registry will be offered to all patients meeting the SNAP trial inclusion criteria. Clinical quality analyses will compare quality-of-care indicators and outcomes adjusted for demographic and prognostic variables between trial sites (or other relevant divisions) for the entire registry cohort (A+B+C+D). Analyses aimed at describing trial representativeness will compare sub-cohort A (SNAP trial participants) to sub-cohorts B+C+D (see section 9.2 below for definition of sub-cohorts).

Figure 1. SNAP-R sub-cohorts



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1. ABBREVIATIONS AND GLOSSARY

ACSQH	Australian Commission on Safety and Quality in Healthcare
AKI	Acute Kidney Injury
AR	Adverse reaction
CKD	Chronic Kidney Disease
CQRs	Clinical Quality Registries
DSMC	Data and Safety Monitoring Committee
DSA	Domain Specific Appendix
eCRF	Electronic case report form
GTSC	Global Trial Steering Committee
MSSA	Methicillin-Susceptible *Staphylococcus aureus*
MRSA	Methicillin-Resistant *Staphylococcus aureus*
NHMRC	National Health and Medical Research Council
Platform	Patients in the platform are those who meet all core eligibility criteria and consent to inclusion in the platform. Occasional patients in the platform will not receive any randomised intervention (if they are not eligible for any available domain).
Platform entry	"Platform entry" is the timepoint when the patient has met core eligibility criteria, given informed consent for the platform, and been randomised
PSSA	Penicillin-Susceptible *Staphylococcus aureus*
PWID	People Who Inject Drugs
Registry	Patients in the registry include all those in the platform (as defined above) PLUS the "registry only" patients. Registry only patients are those who are not in the platform, but who have consented to being in the registry.
RSA	Region Specific Appendix
RTSC	Regional Trial Steering Committee
RWG	SNAP Registry working group
SAB	*Staphylococcus aureus* Bacteraemia
S. aureus	*Staphylococcus aureus*
SNAP	*Staphylococcus aureus* Network Adaptive Platform trial

SNAP-R	SNAP Registry
T2DM	Type 2 diabetes mellitus

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/).

This appendix to the Core Protocol describes the design, operation and analysis of the clinical quality registry that sits adjacent to the SNAP trial domains, and includes both randomised and non-randomised eligible patients with *Staphylococcus aureus* bacteraemia (SAB) at participating sites.

3. SNAP-R APPENDIX VERSION

The version of the SNAP-R Registry Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1.0: Approved by the SNAP Registry working group (RWG) on the 29th of March 2021

Version 2.0: Approved by the SNAP Registry working group (RWG) on the 24th of March 2023

4. SNAP-R GOVERNANCE

4.1. Working group members

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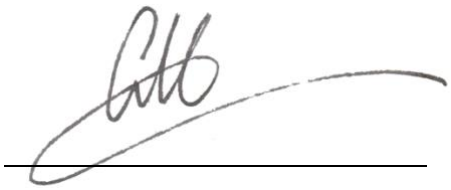
5. SNAP-R WORKING GROUP AUTHORISATION

The SNAP-R Working Group (RWG) have read the appendix and authorise it as the official SNAP Registry Appendix for the SNAP trial. Signed on behalf of the committee,

Chair  Date 24MAR2023

George Heriot

6. REGISTRY-SPECIFIC BACKGROUND

Staphylococcus aureus bacteraemia (SAB) is a serious bloodstream infection with an incidence of around 30 per 100 000 person-years (1) that continues to increase (2). The 30-day mortality after SAB is around 20% (1, 3), a large proportion of which appears to be modifiable with improved adherence to evidence-based care processes (4, 5). Despite this evidence, substantial variation in clinical practice persists (4, 6). Some of this variation is unwanted, such as in the use of inappropriate antibiotic therapy or the failure of complete microbiological assessment, but some arises from genuine uncertainties that exist even among expert clinicians (7, 8).

Clinical quality registries (CQRs) have been shown to reduce unwanted practice variation and improve patient outcomes in a range of complex diseases (9). CQRs improve the quality of care by providing credible, risk-adjusted data, allowing clinicians and institutions to assess their care process and outcomes against established benchmarks and the performance of similar institutions. Data generated by CQRs also facilitate ongoing research into the causes of variation in practices and outcomes, and provide a context for the evolution of consensus clinical management guidelines.

Nesting a clinical trial platform within a registry also allows a more detailed assessment of trial cohort representativeness than traditional screening data. The feedback mechanism of a clinical quality registry closes the translational loop by encouraging the adoption of trial findings into clinical practice at trial sites.

7. REGISTRY OBJECTIVES

7.1. Assessing quality of care and outcome

The primary objective of the registry will be to assess indicators of quality of care and 90-day mortality for patients with SAB at participating sites. Results from the SNAP trial will be incorporated as quality of care indicators to provide a measure of research translation at participating sites. Regular casemix-adjusted feedback on patient outcome and quality of care indicators will be provided to participating sites (see section 10.2) to encourage optimal management of all patients.

7.2. Monitoring the use of trial interventions among non-randomised patients

The registry dataset will also be used to monitor the proportion of non-enrolled patients across participating sites who receive SNAP trial interventions as part of usual care. These results will be used to monitor changes in practice that occur during the lifetime of the trial, including the impact of site participation in the SNAP trial on usual care, and the implementation of findings declared at platform domain conclusions.

7.3. Assessing trial representativeness

The registry will also seek to describe the representativeness of patients enrolled into the SNAP trial by collecting epidemiological and disease-specific descriptors of patients with SAB who are not enrolled into the trial. These data will also be used to examine outcome differences between comparable randomised and non-randomised patients. Statistical comparisons will be made to accompany SNAP trial publications to inform these reports.

8. REGISTRY DESIGN

8.1. Participating centres

SNAP-R will be conducted at all SNAP sites who choose to participate in the registry component. Sites may choose to participate in the registry component only without participating in any of the randomised domains.

8.2. Participant identification

Potential participants will be identified through the screening processes used for the SNAP trial at each participating site (see sections 8.2 and 8.3 of the Core Protocol).

8.3. Registry-specific inclusion criteria

Patients are eligible for inclusion in the registry if they meet all of the Core inclusion criteria set out in section 6.5.1 of the Core Protocol (i.e., *Staphylococcus aureus* complex grown from ≥1 blood culture, and admitted to a participating hospital at the time of eligibility assessment).
All patients who are eligible for and provide consent to enter the core platform will also be included in the registry (all data points in the registry will be included in the core platform data collection).

8.4. Registry-specific exclusion criteria

Patients fulfilling any of the exclusion criteria for the SNAP trial (see section 6.5.2 of the Core Protocol) remain eligible for participation in the registry, excepting only re-entry into the registry within 180 days of the index blood culture used to define a previous registry entry.

8.5. Participant consent and withdrawal

8.5.1. Written informed consent

All potential registry participants will be directly approached for consent during their index hospitalisation. Patients enrolling into the SNAP trial will provide consent for registry processes as part of consent to participate in the SNAP trial. Other patients will be asked to consent to the registry processes only as described below.

Consent for participation in SNAP-R will accord with local jurisdictional requirements. General principles to guide the consent procedures in local jurisdictions are discussed below and further details can be found in the Region-Specific Appendices.

Written informed consent will be obtained from all participants or their surrogate decision makers prior to entry into the registry. Where a potential participant is competent to give consent, they will be directly approached for a consent discussion. An interpreter should be utilised where required, and this will be documented on the consent form.

If a participant does not have the capacity to consent to the participation in the registry (e.g., due to delirium or sedation), then a surrogate decision maker will be approached for consent / assent if

regulatory and legal frameworks allow it in the relevant jurisdiction. Where a surrogate decision maker has provided consent / assent, the participant themselves will be approached to confirm consent (or withdraw) as soon as practicable if they regain capacity. Capacity to consent will be judged by the site investigator using their clinical expertise and in discussion with the treating clinical team.

Deferred consent strategies may be used in jurisdictions where local regulations permit. This would apply to patients who are severely ill and for whom a surrogate cannot be identified in a timely fashion. Deferred consent would be subject to standard participant or surrogate consent as soon as possible thereafter. Issues relating to consent and assent of children will be detailed in a Paediatric Specific Appendix.

8.5.2. Inclusion of deceased people

Where permissible under local requirements, a waiver of consent will be sought for the inclusion of patients with SAB who die during their index hospitalisation prior to being approached for consent as described above.

8.5.3. Withdrawal of consent

Consent for participation in the registry only component can be withdrawn at any time. After notification of withdrawn consent is received, no further health data pertaining to the participant will be collected from any source. All data collected for that participant will be removed from the registry.

8.6. Data collection and storage

All data collection and storage will be conducted using the processes of the SNAP trial, as described in sections 8.11 and 8.12 of the Core Protocol. A specific eCRF will be developed for patients participating in the registry but not the trial.

8.6.1. Data collection stages

Data for the registry will be collected in two stages: i) during the index hospitalisation (corresponding to section 8.8.6 of the Core Protocol); and ii) at or around 90 days (where feasible) and/or prior to the end of each registry reporting period by data linkage (where feasible).

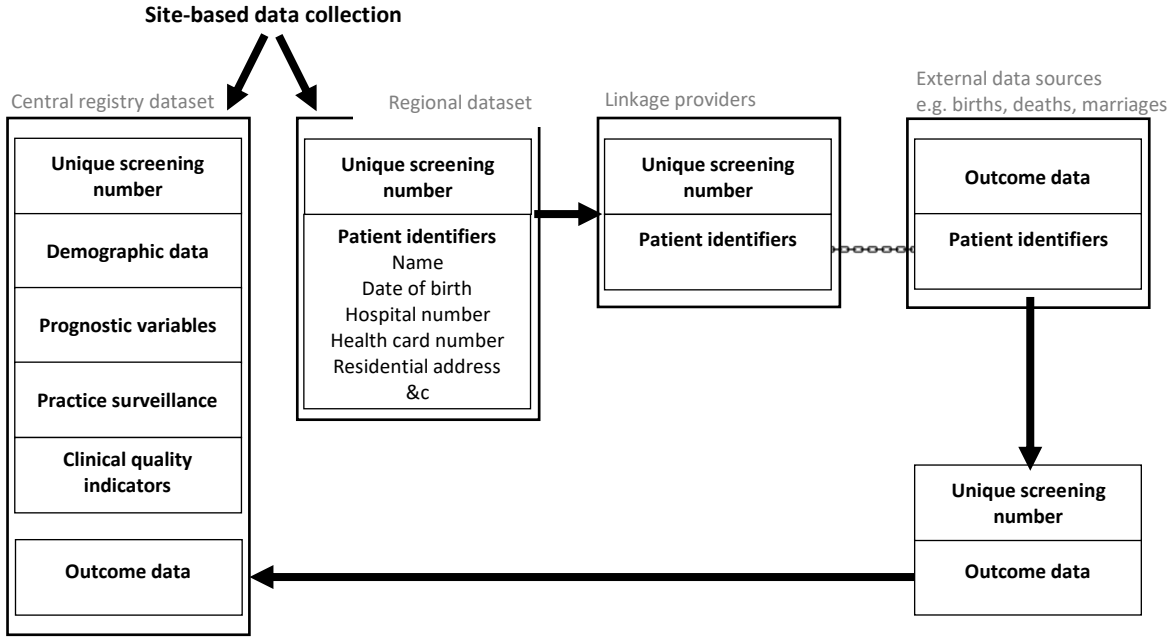
8.6.2. Linkage

Outcome data for registry analyses will be obtained through data linkage for all jurisdictions where it is possible and feasible. Linkage requests will include participants enrolled in the SNAP trial (i.e., in addition

to outcome data abstracted from the source documents described in section 8.12.1 of the Core Protocol) to ensure comparability of outcome data across trial and non-trial (registry-only) participants. For SNAP trial participants, this acts as an additional validation of trial collected outcome data.

Linkage requests will be made prior to the end of each registry reporting period. The necessary patient data for linkage (available only to regional study personnel, see section 8.7.1 below and section 8.12.3 of the Core Protocol) will be submitted to linkage providers in each jurisdiction. Once obtained, the identifying information accompanying outcome data will be replaced with participants' trial identifiers by regional study personnel prior to transmission to the centralised trial administration for inclusion in the database and analysis. Figure 2 presents the data flow and database separation in this process.

Figure 2. Data flows for outcome data obtained by data linkage



8.7. Registry data elements

All data elements are defined by the SNAP trial's data dictionary and are governed by the global trial steering committee (see section 3.1 of the Core Protocol). Changes to these data elements will be made through a data element variation process. The data elements used for registry analyses will be:

8.7.1. Data used for data linkage requests

Data used for data linkage requests (patient identifiers) will be held securely by sites or region using local secure databases. These data will be separated from the central platform database where other data will be held in a re-identifiable format using a unique screening number. Data required for linkage requests (linkage identifiers) will vary between jurisdictions based on the requirements of local linkage providers, but are anticipated to include:

- patient's full name
- sex
- date of birth
- hospital unique identifying numbers
- healthcard number
- residential post code

8.7.2. Demographic data

Demographic data collected for registry analyses will include:

- patients' sex
- date of birth for derivation at age in years, or simply age in years at registry entry
- dates of index blood culture and index hospital admission (for calculation of outcome landmarks and nosocomial bacteraemia categorisation)

8.7.3. Prognostic variables

Prognostic variables used for casemix adjustment will include:

- patient's age at index blood culture (derived variable)
- selected comorbidities (e.g. Diabetes, CKD, liver cirrhosis, cancer, dementia)
- Pitt bacteremia score (10)
- person who injects drugs status
- "community onset" (index blood culture collected within 48 hours of hospital admission) vs. "nosocomial onset" (index blood culture collected 48 hours or more after hospital admission) bacteraemia (derived variable)
- "complicated" vs. "uncomplicated" bacteraemia (see section 6.3.1 of the Core Protocol)
- foci of infection

8.7.4. Practice surveillance

The initial variables describing the use of SNAP trial interventions in non-randomised patients will include:

- definitive "backbone" antibiotic therapy, defined as administration on at least four calendar days in the first seven after collection of the index blood culture of the following agents (day of index blood culture collection is day 1):
    - for penicillin-susceptible *S. aureus* (PSSA): benzylpenicillin, amoxycillin, (flu)cloxacillin, oxacillin, nafcillin, or cefazolin
    - for penicillin-resistant methicillin-susceptible *S. aureus* (MSSA): (flu)cloxacillin, oxacillin, nafcillin, or cefazolin
    - for methicillin-resistant *S. aureus* (MRSA): vancomycin, daptomycin, linezolid, or ceftaroline
- use of adjunctive clindamycin, defined as administration on at least two calendar days in the first seven days from the collection of the index blood culture (where day of collection is considered day 1)
- duration and route of continuing antibiotic therapy:
    - administration of any antibiotic therapy active against the index isolate beyond day 7 after collection of the index blood culture (binary)
        - administration of any intravenous antibiotic therapy active against the index isolate beyond day 7 after collection of the index blood culture (binary)
    - administration of any antibiotic therapy active against the index isolate beyond day 14 after collection of the index blood culture (binary)
        - administration of any intravenous antibiotic therapy active against the index isolate beyond day 14 after collection of the index blood culture (binary)

8.7.5. Clinical quality indicators

The initial clinical quality indicators collected for inter-site comparisons will include:

- collection of repeat blood cultures on calendar days 3 or 4 following collection of the index blood culture
- documented review by an infectious diseases specialist during index hospitalisation
- performance of transthoracic echocardiography during index hospitalisation
- performance of transoesophageal echocardiography during index hospitalisation
- performance of whole-body FDG PET/CT during index hospitalisation

- provision of optimal early antibiotic therapy, defined as at least four calendar days during the first 7 calendar days following collection of the index blood culture where one of the following agents was administered intravenously (derived from data collected above):
    - for penicillin-susceptible *S. aureus* (PSSA): benzylpenicillin, amoxycillin, (flu)cloxacillin, oxacillin, nafcillin, or cefazolin
    - for penicillin-resistant methicillin-susceptible *S. aureus* (MSSA): (flu)cloxacillin, oxacillin, nafcillin, or cefazolin
    - for methicillin-resistant *S. aureus* (MRSA): vancomycin, daptomycin, linezolid, or ceftaroline

8.7.6. Outcome data

The outcome endpoint for registry analyses will be all-cause mortality at 90 days after collection of the index blood culture (see section 8.3 above) as assessed by patient contact, record review, or data linkage where possible and feasible (see section 8.6.2 above). This is not necessarily the same outcome as in the SNAP trial (which assesses mortality from source documents at 90 days after *platform entry*, see section 6.8.1 of the Core Protocol). The secondary endpoint will be duration of survival censored at 90 days after a patient has met the core inclusion criteria.

9. DATA ANALYSIS

9.1. Data extracts

Non-re-identifiable data extracts (i.e., with unique screening numbers removed) will be provided to the registry working group (see section 9 of the Core Protocol) every 12 months. Registry data for patients receiving randomised interventions within the SNAP platform will not reveal allocation status for randomised interventions.

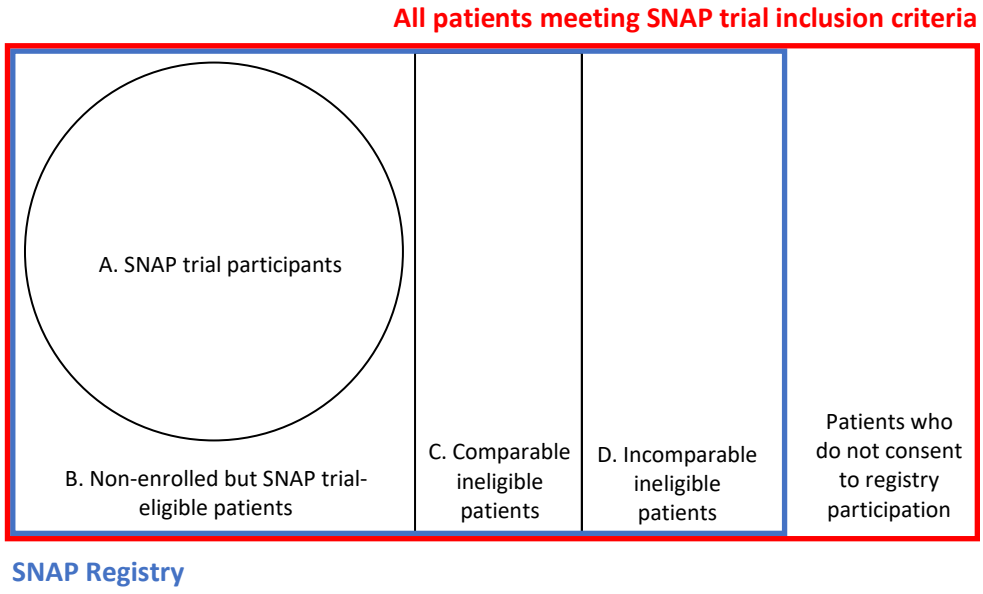
9.2. Sub-cohorts

The broad SNAP-R inclusion criteria will result in multiple sub-cohorts of participants being included in the registry dataset. Not every sub-cohort will be appropriate to include in all registry analyses due to non-comparable clinical features. The registry sub-cohorts are presented in Figure 1 (reproduced from the

Summary above) and are defined by the SNAP trial core exclusion criteria (see section 6.5.2 of the Core Protocol):

- Sub-cohort A is comprised of registry participants who do not meet any of the SNAP trial core exclusion criteria *and* have been enrolled into the trial.
- Sub-cohort B is comprised of participants who do not meet any of the SNAP trial core exclusion criteria but *have not* been enrolled into the trial due to refusal of consent or domain unavailability at their treating site.
- Sub-cohort C is comprised of participants who were excluded from the SNAP trial due to the non-disease-related characteristics described by core exclusion criterion 1 (time of anticipated platform entry is greater than 72 hours post collection of the index blood culture), core exclusion criterion 6 (treating team deems enrolment in the study is not in the best interest of the patient) or core exclusion criterion 9 (patient <18 years of age and paediatric trial recruitment not approved at recruiting site).
- Sub-cohort D is comprised of participants who were excluded from the SNAP trial due to the disease-related characteristics described by all other core exclusion criteria (e.g. polymicrobial bacteraemia, previous participation in SNAP, or anticipated poor prognosis).

Figure 1. SNAP-R sub-cohorts



9.3. Analyses

9.3.1. Quality-of-care and outcome analysis

The performance of clinical quality indicators (including the implementation of SNAP trial results, see section 8.7.4 above) and patient outcomes (section 8.7.5 above) will be compared between sites and regions (with sufficiently large datasets) adjusted for demographic (section 8.7.2) and prognostic (8.7.3) variables for the entire registry cohort (sub-cohorts A-D).

9.3.2. Practice surveillance

The application of SNAP trial interventions in non-randomised patients will be compared between sites and over time for the trial-comparable registry patients (sub-cohorts B and C)

9.3.3. Trial representativeness analyses

Demographic, prognostic and outcome data aggregated from all sites for cohort A (trial participants) will be compared to those for sub-cohorts B-D (non-randomised, registry-consenting patients). These analyses may be presented alongside trial screening data to assess the proportion of all screened patients included in the registry.

9.3.4. Benefit of randomisation analyses

Outcome data aggregated from all sites for cohort A (trial participants) will be compared to those from sub cohorts B and C (non-randomised but clinically comparable patients) after adjustment for demographic and prognostic data.

10. REPORTING

A range of reports will be prepared from the analyses described in section 9 by the registry working group:

10.1. Public reports

In line with the Australian Commission on Safety and Quality in Healthcare's operating principles for clinical quality registries (11), the SNAP Registry will produce regular public reports. These reports will provide comprehensive summaries of the data held by the registry, including participant numbers and characteristics, and aggregated clinical quality indicator and outcome data. Data released as part of

registry reports will be limited by the SNAP Publication Policy. Comparisons between sites and regions will not be included in these reports. Public reports will be available on the SNAP trial website.

10.2. Confidential reports to sites

Confidential reports will be prepared annually for participating sites. These reports will add to the data presented in the public reports by including casemix-adjusted comparisons of clinical quality indicator and outcome data between the sites and regions. In these reports, site-specific data will be made non-identifiable through the use of site codes. Each site's code will be made available to that site's trial PI only.

Outlier status for casemix-adjusted patient outcome will be assessed only for institutions with sufficient data once the registry achieves maturity. A policy for the notification and expected management of outlier institutions will be developed by the registry working group.

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