
# Sub Study:

# SNOOPY (*Staphylococcus aureus* Network; ultrasOund for diagnOsis of endovascular disease in Paediatrics and Youth)

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

**Summary**

*Staphylococcus aureus* bloodstream infection (SAB) is a major public health problem, with 20% of children with SAB requiring intensive care admission. Children with more than one site of infection, including blood clots in veins or arteries, have poorer outcomes. Limited information is available about blood clots associated with SAB in children. This is because SAB guidelines do not include ultrasound imaging for blood clot detection. *Staphylococcus aureus* Network; ultrasOund for diagnOsis of endovascular disease in Paediatrics and Youth (SNOOPY) will be the first study to evaluate whole-body doppler ultrasound, in children with SAB. Participants in SNOOPY will be recruited from the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial over a one year period. SNAP-PY (*Staphylococcus aureus* Network Adaptive Platform - Paediatric and Youth) is the paediatric arm of the SNAP trial, a multi-centre, adaptive platform trial aiming to improve patient outcomes for individuals with SAB. SNOOPY aims to investigate how often blood clots occur, why clots occur (risk factors) and determine how well children tolerate whole-body ultrasound. SNOOPY will assess the feasibility and direction for future expansion to other SNAP-PY sites. Once trialled at participating study sites, SNOOPY may become an intervention in the SNAP trial, where participants will be randomised to ultrasound screening or not, examining the impact of early blood clot detection, compared with standard of care on paediatric SAB clinical outcomes.

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# 1. ABBREVIATIONS

| | |
|---|---|
| AKI | Acute Kidney Injury |
| DSA | Domain-Specific Appendix |
| DSWG | Domain-Specific Working Group |
| DSMC | Data and Safety Monitoring Committee |
| DUS | Doppler Ultrasound |
| GTSC | Global Trial Steering Committee |
| HITH | Hospital in the home |
| IE | Infective Endocarditis |
| ICU | Intensive Care Unit |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| MSSA | Methicillin-susceptible *Staphylococcus aureus* |
| MIC | Minimum Inhibitory Concentration |
| OPAT | Outpatient Antimicrobial Therapy |
| PSSA | Penicillin-susceptible *Staphylococcus aureus* |
| RAR | Response Adaptive Randomization |
| RCT | Randomized Controlled Trial |
| SAE | Serious Adverse Event |
| SNAP | *Staphylococcus aureus* Network Adaptive Platform trial |
| SNOOPY | *Staphylococcus aureus* Network; ultrasOund for diagnOsis of endovascular disease in Paediatrics and Youth |
| SOC | Standard of Care |

# 2. SUB STUDY GOVERNANCE

## *2.1. Sub Study Members*

**Sub Study Lead(s):** Dr Anita Campbell

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**Members:** Prof Steven Tong; Prof Josh Davis; A/Prof Asha Bowen; Ms Leanne Lamborn; Prof Derek Roebuck; Dr Tina Carter; Dr Julie Marsh; Dr Kate Stannage; Prof Chris Blyth; Dr Brendan McMullan; A/Prof Phil Britton; Miss Keerthi Anpalagan

**Proposed 1st Author:** Miss Keerthi Anpalagan

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## *2.2. Contact Details*

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# 3. BACKGROUND AND RATIONALE

## *3.1. Sub study definition*

*Staphylococcus aureus* Network; ultrasOund for diagnOsis of endovascular disease in Paediatrics and Youth (SNOOPY) aims to investigate how often venous thrombosis occurs, risk factors for venous thrombosis and define children at the highest risk to recommend for targeted ultrasound screening. SNOOPY will provide a feasibility assessment and direction for future expansion to other paediatric sites in SNAP-PY to evaluate whether earlier detection and standard of care (SOC) management of thrombosis impacts clinical outcomes.

## *3.2. Sub study background*

Venous thrombosis incidence based on observational data is likely underestimated [1]. The reported incidence is approximately 5-6% in children with SAB [2, 3] and osteomyelitis [4, 5] respectively, and up to 30% in higher risk children with osteomyelitis of the proximal upper/lower extremity, pelvic or vertebral regions. [6, 7] Previous studies have illustrated that a key predictor of paediatric SAB mortality and poor outcomes was multifocal infection associated with endovascular disease. [2, 8-10] Children, unlike adults, are almost as likely to get venous thrombosis (21/353, 5%) as they are infective endocarditis (23/353, 7%) [2], yet current guidelines focus on imaging that is targeted at detecting bone and joint infective foci or infective endocarditis, but not endovascular thrombosis. There is currently minimal recognition of the role doppler ultrasound imaging may have for the detection of thrombosis as a potential infective source for paediatric SAB. [2, 11]

SNOOPY will be the first study to evaluate whole-body doppler ultrasound (DUS), in children with SAB. Eligible participants will include all children aged <18 years with SAB enrolled in the SNAP trial platform or registry only.

# 4. SUB STUDY DESIGN

This sub study will be conducted as part of the SNAP trial. The sub study design is a non-randomised interventional study.

DUS screening will be performed on all children with SAB presenting to the participating site enrolled in the SNAP platform and/or registry for the period of one year. The whole-body DUS will be performed by sonographers or radiology registrars/consultants, and the ultrasound report will be

authorised by a paediatric radiologist consultant. Examination of the clinical signs and symptoms of thrombus will be performed by the study doctor or research nurse.

DUS will be performed in order of priority anatomical sites based on likelihood of thrombus occurrence: [6]

1) site(s) of known bone or joint infection (s)
2) site(s) of CVC(s)
3) groin to knee region
4) pelvic region
5) limited upper abdomen region
6) elbow to subclavian vein region

The first DUS will be conducted as early as possible after enrolment in the SNAP platform and/or registry. A repeat DUS will occur within 72 hours of the initial scan as part of the study in the setting of a previously negative DUS and: i) ongoing SAB or ii) new SAB foci detected clinically or on imaging, in the 72 hours after the initial ultrasound. Most children with SAB will only have only a single positive blood culture[2], so we predict that most children in this study will have a single DUS performed.

Along with demographic, clinical progress and patient outcome data collected through SNAP, additional data to be collected will include patient risk factors for thrombosis, anatomical site(s) of thrombus, length and degree of vessel occlusion, association with a central venous catheter (CVC) or contiguous site of SAB infection, clinical symptoms/signs of thrombus and other infective SAB foci including the presence of necrotising pneumonia, pulmonary emboli, infective endocarditis or cerebral mycotic aneurysm. Acceptability of the procedure will be recorded including imaging completion and reason for non-completion by the parent, sonographer and/or radiologist. Results of any thrombophilia screen and thrombus management conducted as part of SOC according to international consensus guidelines, [12] will be recorded.

## *4.1. Population*

Children aged < 18 years of age with SAB, enrolled in the SNAP platform and/or registry at study sites will be eligible for recruitment for a period of one year from the initiation of the sub-study.

## *4.2. Eligibility criteria*

Patients are eligible for this sub study if they meet all of the platform or registry-level inclusion and none of the platform or registry-level exclusion criteria AND all of the sub study inclusion and none of the sub study exclusion criteria outlined below.

#### 4.2.1. Sub study inclusion criteria

1) < 18 years of age

#### 4.2.2. Sub study exclusion criteria

Patients will be excluded from this sub study if they have any of the following:

1) Treating clinician deems not in the best interest of the participant
2) Time from blood index collection is >120 hours

## *4.3. Interventions*

#### 4.3.1. Sub Study Intervention

All participants will be assigned to receive the following intervention.

- Whole body doppler ultrasound (DUS)

#### 4.3.2. Timing of initiation of whole body doppler ultrasound imaging

DUS will be conducted as early as possible (either on day 1 or day 2 after enrolment in SNAP). A repeat DUS will occur within 72 hours (+/- 24 hours) of the initial scan in the setting of a previously negative DUS and:

i) ongoing SAB

or

ii) new SAB foci detected clinically or on imaging

## *4.4. Concomitant care*

As per usual care and, if participating, as allocated within domains in SNAP platform

## *4.5. Endpoints*

#### 4.5.1. Primary sub study endpoint

The primary endpoint for this sub study is:

Thrombosis detected on DUS screening that results in a clinically significant change in management for SAB within 2 weeks of initial DUS procedure, inclusive of ≥1 of the following:

i) commencement of anticoagulation therapy,
ii) surgical thrombus management,
iii) central venous catheter (CVC) removal/replacement due to thrombus detection.

#### 4.5.2. Secondary sub study endpoints

The secondary endpoints for this sub study will be:

- Feasibility of DUS in paediatric SAB by reporting the portion of incomplete versus complete imaging studies, time taken to complete imaging, and the parental acceptability of the whole-body DUS (measured using a Likert scale).
- Identification of clinical variables associated with thrombosis.
- Investigation of the differences in clinical outcomes including duration of bacteraemia and length of hospitalisation in children with clinically significant thrombosis detected, compared to those without.

# 5. SUB STUDY CONDUCT

## *5.1. Sub study-specific data collection*

#### 5.1.1. Clinical data and sample collection

Additional sub study-specific data will be collected from the patient's medical, laboratory, radiology records and/or verbally from participants and/or their guardians:

- Patient risk factors for thrombosis
- Anatomical site (s) of thrombus
- Length and degree of vessel occlusion
- Association with a CVC or contiguous site of SAB infection
- Standard of care thrombophilia testing and management
- Line removal
- Clinical sign and symptoms of thrombus

#### 5.1.2. Sub study-specific study timeline

In addition to data collection as per the SNAP trial Core protocol, the sub-study data collection points are outlined below.

**Table 1: Sub study-specific schedule of visits and follow-up**

| Sub study Day | Day 1 | Day 2 | Day 3-5 | Day 8 | Acute Discharge |
|---|---|---|---|---|---|
| Eligibility and obtain consent#<br>#Eligibility to be assessed and consent obtained at the same time as the SNAP platform or registry only | X | | | | |
| Whole body doppler ultrasound (DUS)<br>*if previously negative DUS and: i) ongoing SAB or ii) new SAB foci detected clinically or on imaging, within 72 hours after the initial ultrasound. | X | X<br>If first DUS was not done/not able to be performed on day 1 | +/- * | | |
| Collect data as per sub study CRF | X | X | X | X | X |

### *5.2. Blinding*

Not relevant.

#### 5.2.1. Unblinding

Not relevant.

## 6. Data Analysis Plan

Descriptive statistics will be used to characterize and describe the distributions of the variables collected in this study. Then, a multivariable logistic regression model will be used to investigate the relationship between multiple independent variables such as (site of foci, days of bacteraemia) and the sub-study primary endpoint. The multivariable logistic regression model will take form as:

$$\log\left(\frac{\pi_i}{1-\pi_i}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n$$

The β coefficient, 95% confidence interval (CI) and/or the p-value will be presented in statistical models adjusted for confounding variables. A 95% CI value of >1 would suggest that the factor/variable is positively associated with the outcome (i.e., it increases the risk of clinically relevant thrombosis).

# 7. STATISTICAL CONSIDERATIONS

## *7.1. Statistical modelling*

### 7.1.1. Primary model

None.

## *7.2. Interactions with interventions in the SNAP trial domains*

There is a possibility that treatment of thrombosis may cause children to recover faster, or clear bacteraemia more rapidly. We predict that the likelihood of these events occurring are low to unlikely.

## *7.3. Potential impact on trial integrity if findings released prior to overall platform conclusions are reached*

The manuscript will report on DUS results and not overall SNAP trial results (i.e., 90-day outcomes are not required for this study). Due to the small participant number (approximately 80-100 participants) for this study, only a small subset of the overall trial population will be included. Please refer to the SNAP Authorship and Publications Policy for further information.

# 8. ETHICAL CONSIDERATIONS

## *8.1. Potential sub study-specific adverse events*

The consultant haematologists will oversee treatment of thrombosis at each site as per standard of care. The most serious side effect of anti-coagulation includes bleeding in the following sites which will be collected in the SNOOPY CRF:

- Gastrointestinal tract
- Pericardial tamponade
- Retroperitoneal hematoma
- Intracranial bleeding

- Hemothorax

If these adverse events do occur, they will be managed by the treating team in collaboration with a haematologist.

### *8.2. Sub study-specific consent issues*

SNAP-PY participants will be offered the opportunity to participate in SNOOPY. Consent to SNOOPY will be opt-in and harmonised with overall SNAP-PY consent processes.

## 9. GOVERNANCE ISSUES

### *9.1. Proposed budget*

The proposed budget for SNOOPY includes funds to cover: 1) sonographers and radiologists to conduct and report whole-body DUS; 2) community engagement, including the development of trial resources, review of study progress and translation plans; 3) statistical support.

- Whole body doppler ultrasound scans for one year at study sites ($200 per whole body doppler ultrasound scan per child) 110 scans = $22,000
- Community engagement including recruitment, study participant resource development and translation of research findings: A WA community reference group will consist of ~4 members. The reference group members will be paid an honorarium payment of $50/hour (inc. parking). Four two-hour community reference group meetings will be held per year, with one hour of pre- reading before each meeting. $50/hour x 3 hours x 4 members x 4 meetings per year = $2,400. Light catering will be provided per meeting at $60 a meeting ($60 x 4 meetings = $240). Therefore, $2400 + $240 = $2,640
- Statistical support and data management: $135/hr $750/day for 4 days = $3000
  In kind data management and analysis support provided by PhD student Keerthi Anpalagan for whom this proposal comprises a major project within her PhD. Keerthi is funded by a postgraduate award and UWA postgraduate scholarship.
  Total costs = $25,000

### *9.2. Funding of sub study*

Applications for funding have been made to the Australasian Society for Infectious Diseases. We are submitting this protocol for ethics consideration in anticipation that funding becomes available. The study won't proceed until sufficient funds are available.

## *9.3. Proposed timeline*

| | |
|---|---|
| Approval of SNOOPY as a sub-study of SNAPPY by the SNAP Global Trial Steering Committee | Completed - September 2022 |
| Development of the finalised SNOOPY sub-study protocol | September – February 2023 |
| Amendment to central ethics at Royal Melbourne Hospital, and governance approvals at study sites | February 2023 – June 2023 |
| Build and test additional REDCap electronic data record for SNOOPY for data collection in addition to the SNAP trial database infrastructure | December 2022- April 2023 |
| Recruitment of participants for the SNOOPY study who have consented to the SNAP-PY registry at study sites | July 2023 - June 2024 |
| Interim analysis after 6 months of data collection | September 2023 – December 2023 |
| Apply for an NHMRC Clinical Trials and Cohort Studies Grant to fund expansion of SNOOPY other SNAP-PY sites | July 2023 - August 2023 |
| Abstract submission for Antimicrobials (ASA) and the International Symposium on Staphylococci and Staphylococcal Infections (ISSI) | October - December 2023 |
| Data cleaning and Final analysis after one year of data collection | June 2024 |
| Prepare manuscript for submission | August 2024 |
| Expansion of SNOOPY to other SNAP-PY sites | 2024- 2027 |

## *9.4. Sub study-specific declarations of interest*

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

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