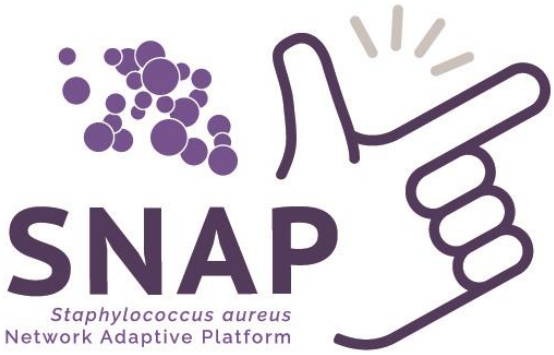

People Who Inject Drugs (PWID)-Specific Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

PWID-Specific Appendix Version 2.0 dated 24 March 2023

Summary

This appendix to the SNAP Core Protocol describes additions relevant to the cohort of SNAP participants who inject drugs.

Aims of this PWID-specific protocol are to:

1. Support the implementation of a sub-group analysis of the SNAP Core Protocol in PWIDs
2. Characterise the PWID population within the SNAP cohort and registry
3. Determine patient- and site-level predictors of the study primary and secondary outcomes (including premature discharge and readmission within 90 days [data linkage]) within the PWID population

SNAP: Synopsis of PWID specific protocol adaptations	
	SNAP PROTOCOL
TITLE	*Staphylococcus aureus* Network Adaptive Platform trial (SNAP)
BACKGROUND	*Staphylococcus aureus* bacteraemia (SAB) is a common and severe infection with a 90-day mortality of 15-30% 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. PWID comprise an important subset of SAB patients at particularly high risk of poor outcomes. The PWID specific adaptation of SNAP aims to collect specific data of interest in this sub-group with the aim of better understanding predictors of outcomes and the optimal therapeutic regimens in this group.
ENDPOINTS	Primary platform endpoint: All-cause mortality 90 days from platform entry. Secondary core platform endpoints: refer to Core Protocol Section 6.8 Secondary PWID-specific endpoints: 1. Premature discharge 2. Readmission to hospital within 90-day study period [obtained from linked hospital admitted episode datasets]
PLATFORM SPECIFIC INCLUSIONS	These are the same as for the overall Core Protocol Section 6.5. 1. PWID will be defined as having injected drugs within the 6 months prior to platform eligibility assessment.
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 PWID participants.
STUDY DURATION	May 2021 onwards
NUMBER OF PARTICIPANTS	The initial trial funding and infrastructure will aim to enrol up to 6,000 participants into the platform. Not powered for sub-group analysis however it is estimated that PWID will contribute up to 20-30% of overall study population, thus allowing for potential specific

	subgroup analysis. Harmonised outcome reporting will allow for meta-analysis with international studies.

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1. ABBREVIATIONS

BBV	Blood-borne viruses
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMC	Data and Safety and Monitoring Committee
GTSC	Global Trial Steering Committee
HCV	Hepatitis C Virus
HITH	Hospital in the Home
IDU	Injecting Drug Use
IRID	Injecting Related Infectious Disease
LOS	Length of Stay
OD	Odds Ratio
PWID	People Who Inject Drugs
RSA	Region-Specific Appendix
SAB	*Staphylococcus aureus* bacteraemia

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. PWID-SPECIFIC APPENDIX VERSION

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

3.1. *Version history*

Version 1.0: Approved by the PWID Working Group on the 29th of March 2021

Version 2.0: Approved by the PWID Working Group on the 24th of March 2023

4. PWID-SPECIFIC WORKING GROUP GOVERNANCE

4.1. *Members*

Chairs:	Prof Gail Matthews (Sydney, AU)
	A/Prof Andrew Stewardson (Melbourne, AU)
Members	Prof Eugene Athan (Geelong, AU)
	Dr Marianne Martinello (Sydney, AU)
	A/Prof Archana Sud (Sydney, AU)
	Dr Terry Wuerz (Winnipeg, CA)
	Prof Steven Tong (Melbourne, AU)
	Prof Joshua Davis (Newcastle, AU)
	Prof Adrian Dunlop (Sydney, AU)
	Dr Carly Botheras (Geelong, AU)
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	Consumer representative (TBD)

4.2. *Contact Details*

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5. PWID WORKING GROUP AUTHORISATION

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

Chair Prof Gail Matthews _____ Date 24/03/2023

6. BACKGROUND AND RATIONALE

6.1. *Introduction*

People who inject drugs (PWID) are at high risk of admission to hospital with an injecting related infectious disease (IRID) such as cellulitis, endocarditis, osteomyelitis etc (1). S*. aureus* is the most common causative organism (2). *S. aureus* bacteraemia (SAB) is a significant and life-threatening condition in the general population and occurs frequently in people who are currently injecting drugs due to the potential for direct inoculation. It is estimated that 25-30% of admissions for SAB are in PWID (although this number is likely to be higher due to lack of disclosure), and the overall risk of SAB in the PWID population is up to 16 x higher than the general population. Not only is SAB more common in PWID, it is also associated with significant morbidity (3). The mortality rate is estimated at 8-10% and generally lower compared to non-PWID in part due to the younger age and the fewer medical co-morbidities of this group.

Current treatment guidelines for SAB recommend a minimum of 2 weeks intravenous antibiotics with extension for difficult or complex infection, including many IRID. The necessity to complete this course as an inpatient, particularly given reluctance to use Hospital in the Home (HITH) type services for this population raises specific challenges (4).

Rates of premature discharge (which we use to include the terms, 'discharge against medical advice' and 'elopement') in PWID are elevated compared to non-PWID. In a recent analysis of treatment completion rates for 106 patients with SAB at a single site in Sydney, 46% (16/35) of PWID failed to complete treatment due to premature discharge compared to 0% (0/71) of non-PWID ($p<0.001$); similarly 34% (12/35) of PWID versus 10% (7/71) of non-PWID had a length of stay (LOS) <14 days (odds ratio [OR] 4.8, 95% CI 1.7-13.6, p=0.002). A higher proportion of PWID were readmitted to hospital within 28 days with positive *S. aureus* cultures (8% versus 0%, p=0.034), and of those PWID who are premature discharged, 81% were readmitted within one year (5).

Reasons for premature discharge are complex and multifactorial, but may relate to poorly controlled pain management and opiate substitution, competing social demands relating to income and housing, and stigma within health care services (6). Among PWID, recent IDU, Aboriginal ancestry, leaving on weekends and welfare check day have been associated, whereas inpatient opioid substitution therapy, social support, older age, and admission to a community-based model of care have been negatively associated with premature discharge (7). Although preventing premature discharge is a significant challenge in a subgroup of PWID, it is also likely that many PWID are not identified as such

routinely in medical notes and there are many PWID who are compliant with treatment regimens and complete a full treatment course without issue. Many of this group are also eminently suitable for HITH type services (8, 9).

Increasingly there is recognition within the medical community of the need to destigmatise PWID and develop a more holistic approach to the provision of inpatient health services for this group (10, 11). Multi-disciplinary teams involving infectious diseases, addiction specialists, pain management and discharge services have been proposed as potential new models of care.

The SNAP study provides an ideal platform to collect essential data in a large sample of PWID undergoing treatment for one of the commonest cause of extended hospital admissions in this group. Data will help inform therapeutic strategies including the utility of early oral switch, plus help define predictors of successful treatment completion guiding future policy directions. Additional immunopathological questions including the role of *S. aureus* antibodies in treatment outcome and the epidemiology of transmission clusters in PWID networks are also possible - as is the development of an active intervention specifically targeted to PWID.

7. AIMS

Aims of the PWID-specific protocol are to:

1. Support the implementation of a sub-group analysis of the SNAP Core Protocol in PWIDs
2. Characterise the PWID population within the SNAP cohort and registry
3. Determine patient- and site-level predictors of the study primary and secondary outcomes (including premature discharge and readmission within 90 days [data linkage]) within the PWID population

8. TRIAL DESIGN

8.1. *PWID-specific criteria*

The following criteria defines who is included in the PWID specific data collection and analyses

- One or more episodes of injecting drug use (non-prescribed) in the 6 months prior to platform eligibility assessment.

8.2. ***Endpoints***

8.2.1. Primary outcome

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

8.2.2. Secondary outcomes

8.2.2.1. Core secondary outcomes

All secondary endpoints as specified in the Core Protocol Section 6.8 remain applicable. In addition, the following endpoints/outcomes will be collected:

1. Premature discharge (yes/no), where premature discharge includes unplanned discharge (i.e., patient chooses to leave hospital before the medical team recommends discharge) and elopement (i.e., patient leaves without telling staff).
2. Readmission to hospital after discharge (self or planned) within 90-day study period (yes/no). This outcome will be obtained subject to linkage with relevant hospital admitted episode datasets. Refer to the SNAP Registry Appendix.

8.2.2.2. Domain specific secondary outcomes

There will be no modification to the domain specific secondary outcomes.

8.2.3. Rationale for the PWID-specific outcome(s)

PWID are a group at particularly high risk of increased morbidity and mortality, often related to negative experiences with delivery of care within health services and typified by early disengagement and suboptimal completion of therapy. Data on factors that may impact on successful completion of therapy in this group are limited. The large sample size of SNAP allows a comprehensive evaluation of variables that may be associated with both negative and positive outcomes including but not limited to drug use characteristics, social determinants and therapeutic engagement with drug and alcohol services

9. TRIAL CONDUCT

9.1. *PWID-specific patient-level data collection*

There are a number of PWID specific data variables that are of interest in SNAP participants identified as PWID based on the eligibility defined in 8.1. In this group, a PWID-specific CRF will be completed at entry to the study, on discharge, and at day 90 (if still in hospital).

Variables of interest that may be collected:

On entry into study:

- Substance use
    - Injecting risk characteristics in the 6 months prior to SAB
    - Received medical care for addiction in past 6 months (prior to hospitalisation)
    - Use and type of opioid replacement therapy on admission
    - Smoking and alcohol history
- Sociodemographic characteristics
    - Homelessness
- Mental health
    - Psychiatric diagnosis other than substance-related and addictive disorders
- Infectious complications of injecting drug use
    - Past-history of injecting related infection
    - BBV co-infection
    - Use and outcome of previous HCV treatment (in those with a prior history of HCV infection)

On discharge

- Assessment by drug and alcohol services during inpatient stay
    - If yes, date of first assessment
- Use and type of opioid replacement therapy during admitted episode
- Use and type of nicotine replacement therapy during admitted episode
- Premature discharge (yes/no)
    - If yes, was a negotiated treatment plan in place (yes/no)

At 90 days (if still in hospital)

- Assessment by drug and alcohol services during inpatient stay
- Assessment by a psychiatrist during inpatient stay
- Use and type of opioid substitution therapy

Data linkage

- Readmission to hospital following discharge
- Death following discharge

10.ETHICAL CONSIDERATIONS

10.1. *PWID-specific consent issues*

There are no PWID specific procedures for obtaining informed consent.

10.2. *Domain specific considerations*

The only domain specific consideration in PWID relates to the early oral switch domain. Enrolment into this may require extra consideration in PWID (issues around adherence, social circumstances, appropriate timing for discharge to home etc). Investigators should be aware of the need to consider these issues carefully before enrolling into this domain. These considerations apply to all patients who are eligible for inclusion and are therefore outlined in the Core Protocol, but they are likely to be particularly relevant to PWID.

11. GOVERNANCE ISSUES

11.1. *Funding of PWID-specific appendix*

Funding sources for SNAP are specified in the Core Protocol.

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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