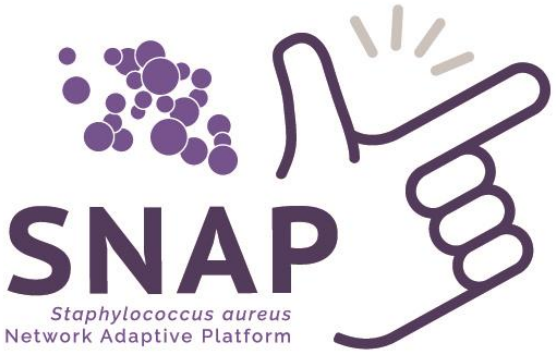

Health Economics Appendix

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Health Economics Appendix Version 2.0 dated 24 March 2023

TABLE OF CONTENTS

1. ABBREVIATIONS AND GLOSSARY

CRF	Case Report Form
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMC	Data Safety and Monitoring Committee
GTSC	Global Trial Steering Committee
HE	Health Economic(s)
ICER	Incremental Cost-Effectiveness Ratios
ICU	Intensive Care Unit
NMB	Net Monetary Benefits
PET/CT	Positron Emission Tomography/Computed Tomography
RSA	Region-Specific Appendix
SAP	Statistical Analysis Appendix
SNAP	*Staphylococcus aureus* Network Adaptive Platform trial

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 (SAP; 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. HEALTH ECONOMICS APPENDIX VERSION

The version of the Health Economics (HE) Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Health Economics Working Group on the 30th of March 2021.

Version 2: Approved by the Health Economics Working Group on the 24 March 2023

4. HEALTH ECONOMICS GOVERNANCE

4.1. Domain members

Chair: Hannah Carter

Members: Prof Josh Davis

Prof Steven Tong

A/Prof Richard De Abreu Lourenco

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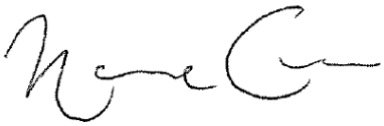
5. HEALTH ECONOMICS WORKING GROUP AUTHORISATION

The Health Economics Working Group have read the appendix and authorise it as the official Health Economics Appendix for the SNAP trial.

Signed on behalf of the committee,



Chair Date 24 March 2023

Hannah Carter

6. BACKGROUND AND AIMS

In the context of scarce health care resources, it is important that funding is directed towards high value treatments. Value can be defined as the level of improvement in patient health outcomes achieved per dollar spent (1). Cost-effectiveness analysis is a method for determining the value of health interventions by comparing the costs and health outcomes of an intervention relative to an alternative, typically 'usual care' (2).

This document outlines the protocol for the economic evaluation to be conducted alongside the SNAP trial. The aim of this study is to identify the treatment regimens that represent the most cost-effective use of health care resources. Changes to the requirements or conduct of a health economic analysis required for the purposes of a specific SNAP domain are specified as appendices to this document. The study will adhere to recommended research practices for cost-effectiveness analysis alongside clinical trials (3).

7. HYPOTHESIS

It is hypothesised that any treatment groups where a statistically significant survival benefit is observed will be cost-effective, and potentially cost-saving. This is due to the relatively inexpensive nature of the treatment drugs, and the potential for substantial years of life gained with effective treatments.

8. METHODS

8.1. Economic evaluation design

A series of cost-effectiveness analyses will be performed for each treatment the trial identifies as being either superior or non-inferior based on the primary outcome of 90-day mortality. The analyses will adopt an intention to treat approach and include all patients recruited to the trial and randomised to the treatments in question. A within-trial analysis will be used to assess differences in costs and outcomes over the trial period, with a modelled extrapolation of survival outcomes post-90 days to account for years of life gained over a lifetime.

8.2. Outcomes

Overall, the outcome of the cost-effectiveness analysis will be the incremental cost per life year gained. Within-trial differences in mortality rates will be informed by the SNAP trial's primary outcome analysis

on 90-day mortality. Long-term survival outcomes will be modelled using Years of Potential Life Lost approach based on patient age and sex at the time of enrolment (4).

All modelled costs and outcomes will be discounted at an annual rate of 5%.

8.3. Data collection

The cost-effectiveness analysis will be informed by trial data on pharmaceutical use, hospital length of stay and patient employment status. It is known that the costs of infection requiring hospitalisation are substantial, with hospital length of stay the major driver of these costs (5-7). However, quantifying the effect of infection on length of stay can be complicated because the exposure is time dependent: infection may prolong hospital stay, while longer stays increase infection risk (8, 9). It is therefore important that the analysis of cost differences between treatment groups compares differences in length of stay post infection, to avoid introducing bias due to pre-infection differences in lengths of stay for those patients who developed an infection while already in hospital. For this evaluation, 'post-infection' will be pragmatically defined as 'post-randomisation', consistent with the commencement of treatment as per the study protocol.

Specific resource use items to be collected within the trial include:

- ***Study pharmaceuticals:*** Selected drug names, dosages and durations of use will be recorded in trial case report forms (CRFs).
- ***Total index hospital admission:*** Length of stay post-randomisation will be estimated based on the difference between hospital discharge date and date of randomisation, as recorded in trial CRFs. Additional data items will capture the length of stay in general wards, ICU, hospital in the home, and rehabilitation facilities.
- ***Readmissions:*** All readmissions within 90 days of randomisation will be recorded as per the index admission, in selected jurisdictions where data linkage is available.
- ***Patient employment impacts:*** Data on labour force status will be collected at baseline and 90 days. The number of days patients have taken off work due to illness with infection will also be recorded at 90 days (see appendix 1).

8.4. Costing perspective and methods

The base case cost-effectiveness analysis will adopt an Australian health system perspective with Australian unit costs applied to pooled resource use data collected from all patients recruited to the study. Separate sub-group analyses will report on country-specific unit costs for New Zealand, Singapore, Canada, Israel, and any new regions that join the study.

Pharmaceutical unit costs will be applied using market prices. Hospital costs will be estimated using an average 'cost per bed day' as a proxy for total hospital costs, stratified by the type of bed day (i.e. general ward, ICU, hospital in the home, rehabilitation) and, where available, incorporating costs associated with inpatient care (e.g., diagnostic, interventional and supportive care). Unit prices for hospital care will be sourced from national hospital pricing policy documentation, or from published literature where national pricing information is unavailable.

The indirect costs associated with patient productivity loss will be investigated in a sensitivity analysis. The human capital approach (10) will be used to value lost work days due to morbidity and mortality. A proxy value of lost income per day will be estimated based on individual patient level data on age, sex, and labour force status, using data from the Australian Survey of Employee Earnings and Hours (11).

8.5. Analysis plan

A Bayesian statistical approach using Monte Carlo simulation techniques will be used to estimate the incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMB) for each treatment comparison. An overarching cost-effectiveness analysis will be performed to compare all superior and non-inferior treatment regimens within each silo.

Incremental costs and outcomes will be measured as the differences in arithmetic means. Multiple imputation techniques will be used to address missing data. Prior distributions will be informed by the observed data where available. Results will be reported as the mean of 10,000 simulations, alongside 95% credible intervals. This approach incorporates the uncertainty inherent in the data with results able to be presented in the form of a probability (e.g. 'there is a 75% chance the intervention is cost-effective'). This is the conventional approach to presenting results within the health economics discipline. It has the advantage of producing results which can be readily understood and interpreted by decision makers.

Consideration will be given to the level of heterogeneity in resource use and treatment effects between countries. If there is evidence of heterogeneity, we will adopt multivariable cost regressions to adjust for country effects in the analysis using the methods described in Cook et al (12).

Joint parameter uncertainty will be represented using probabilistic sensitivity analyses. A series of one-way (deterministic) sensitivity analyses and scenario analyses will also be presented to highlight the impact of key drivers and assumptions on the cost-effectiveness result, including the impacts of changes in unit costs and the discount rate.

9. APPENDIX 1

9.1. Productivity questions

AT BASELINE

1. What is your current labour force status?
    - Employed full time
    - Employed part time
    - Currently looking for work
    - Not currently working and not looking for work
    - Retired

AT 90 DAYS

For patients who were working at baseline:

1. How many days off work have you taken over the past three months due to your illness with a bloodstream infection?

All patients:

2. Has your employment status changed since you were discharged from hospital after infection? (Yes/No/Not yet discharged)

If yes:

3. What is your current labour force status?
    - Employed full time
    - Employed part time
    - Currently looking for work
    - Not currently working and not looking for work
    - Retired

4. If you have a carer who has been working in paid employment, how many days of work have they missed due to their caring responsibilities while you were unwell with a bloodstream infection?

10.APPENDIX 2

10.1. Domain specific HE elements: PET-CT diagnosis of SAB

Hypothesis (ref. 7): The use of PET-CT will be cost-effective (in terms of achieving an acceptable cost per quality adjusted life years, QALYs, gained) compared with usual care for the diagnosis of SAB.

Outcomes (ref. 8.2): The impact on participants' quality of life (QoL) of PET-CT guided diagnosis and treatment for SAB will be assessed using the EUROQoL EQ-5D-5L. Data will be collected at PET/CT domain entry (considered 'baseline') and at platform day 90 among participants in the PET-CT and usual care arms. Country specific utility weights will be applied to value QoL for the purposes of estimating QALYs (the combined impact on the length of life and quality of life) (13). Extrapolation of longer-term survival impacts will be as described in Section 8.2.

Data collection (ref. 8.3):

- ***Time requirement for PET-CT acquisition***: In the SNAP PET domain silo, an assessment of the time required for acquisition of a full body PET-CT in patients with suspected SAB infection is required. This will inform allocation of the relevant cost to the conduct of that procedure within this setting. For this purpose, a representative trial site will be identified within the Australian cohort from which time for scan acquisition can be ascertained from standard metrics (e.g., 'time-stamping' at PET-CT conduct).

Data collection (ref. 8.4): The costs of PET-CT will be estimated using a shadow price for PET-CT conduct based on known prices for scans of a similar complexity and duration as available through the Medicare Benefits Schedule for Australia.

Analysis plan (ref. 8.5): Results of the cost-effectiveness analysis will be expressed as the cost per QALY for PET-CT compared with usual care for SAB detection.

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