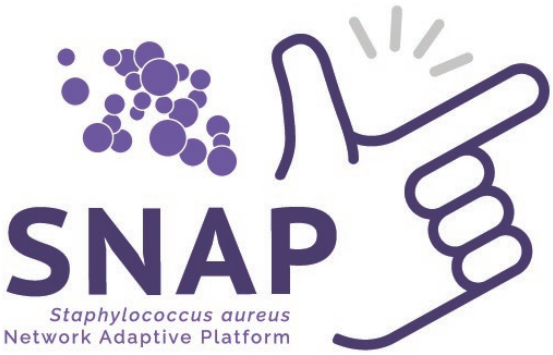


Domain-Specific Appendix:

PET/CT Domain

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

PET/CT Domain-Specific Appendix Version 1.0 dated 27 July 2023

Summary

Participants with *Staphylococcus aureus* bacteraemia (SAB) admitted to participating hospitals will be randomised to receive one of two interventions:

- Usual care with FDG PET/CT
- Usual care with no PET/CT

At this participating site, the following interventions have been selected within this domain:

☐ Usual care with FDG PET/CT

☐ Usual care with no PET/CT

The primary objective is to evaluate the impact of PET/CT on clinical outcomes including 90-day mortality and Desirability of Outcome Ranking (core secondary outcomes).

Secondary objectives are to determine the impact of PET/CT on clinical decision making, antibiotic use (duration and route), detection of infection foci, use of radiological investigations, and health economic costings.

SNAP: PET/CT Domain Summary	
Interventions	• Usual care with FDG PET/CT • Usual care with no PET/CT
Silo, domains, and cells	Domain-eligible participants will be randomised to either PET/CT or no PET/CT. A single population parameter for the domain will be estimated and reported using data pooled across silos.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the early oral switch domain. No other interactions will be evaluated with any other domain.
Randomisation	Participants will be randomised at platform entry in a fixed 1:1 ratio across the domain. A participant's allocated intervention will be revealed at the time that domain-specific eligibility criteria are met at platform day 7 (+/- 2 days), and the assigned arm revealed at this timepoint. Response adaptive randomisation may be applied if additional interventions within this domain are included in future versions of this DSA.
Domain Specific Inclusions	Domain-specific inclusion criteria are: • PET/CT participating site • Patient is accessible for PET/CT – a patient is considered accessible if the site team are able to access the patient medical records, arrange for a PET/CT scan for the patient, and discuss this domain with the patient and their treating healthcare providers.
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • Pregnant – patients of childbearing potential should be assessed for pregnancy status and a pregnancy test performed (if not performed within the past 10 days) • Currently breastfeeding • <18 years of age • Patient has had a PET/CT in past 7 days • Patient needs a PET/CT in the next 7 days (in the opinion of the clinical team, at the time of eligibility assessment) • Clinically unstable for PET/CT (as judged by the treating clinical team, considering need for organ support and capacity to lie flat for the PET/CT) • Contraindication to PET/CT (e.g., claustrophobia, persistently elevated blood sugar levels [>12.5mmol/L] that cannot be corrected) • Patient no longer willing to participate in the domain – in the days leading up to judging eligibility, it may be helpful to discuss with the patient the potential for PET/CT vs no PET/CT to allow imaging planning • Clinician deems participation in this domain is not in the patient's best interests (provide reason)

Intervention-Specific Exclusions	Nil
Endpoints	<u>Primary platform endpoint:</u> All-cause mortality at 90 days. <u>Secondary platform endpoints</u>: refer to Core Protocol Section 6.8 <u>Secondary Domain-specific endpoints:</u> 1. Change in proposed management of *S. aureus* bacteraemia following PET/CT results, comparing proposed management at domain entry and proposed management following receipt of PET/CT results (this outcome is relevant to PET/CT arm only) 2. Change in management of *S. aureus* bacteraemia, comparing proposed management at domain entry and actual management during the total hospital admission (this outcome is relevant to both PET/CT and no PET/CT arms) 3. Diagnosis of new infection foci between domain entry and platform day 14 4. Total imaging investigations between domain entry and total hospital discharge 5. Estimated total radiation exposure between domain entry and total hospital discharge 6. Total diagnostic and source control procedures between domain entry and total hospital discharge 7. Health economic cost analysis specific to the PET/CT domain as detailed in the Health Economic appendix. 8. Total incidental diagnoses made via any imaging investigations, including PET/CT, from domain entry to total hospital discharge 9. Serious Adverse Events (SAEs) that occur as a consequence of any imaging investigation or radiology procedure undertaken from domain entry to total hospital discharge
Decision criteria	The primary objective for this domain is to determine if routine PET-CT is **superior** to control (no routine PET-CT). Superiority is defined as an OR < 1 for the primary endpoint (where an OR > 1 indicates an increase in mortality for the intervention compared to the control). There are no plans for a scheduled analysis prior to reaching a sample size of 820 because smaller sample sizes are unlikely to provide sufficient precision for estimates of the intervention effect.
Pre-specified subgroup analyses	i) Low risk vs high risk bacteraemia (as defined at time of eligibility assessment for domain entry) ii) Primary bloodstream infection (i.e., unknown focus of infection at the time of domain eligibility assessment) versus other iii) Nosocomial (index blood culture collected >48h after hospital admission) vs community onset bacteraemia

TABLE OF CONTENTS

1. ABBREVIATIONS

aOR	Adjusted Odds Ratio
CRF	Case Report Form
DOOR	Desirability of Outcome Ranking
DSA	Domain-Specific Appendix
DSMC	Data Safety and Monitoring Committee
DSWG	Domain-Specific Working Group
FDG	Fluoro-2-deoxy-D-glucose
GTSC	Global Trial Steering Committee
ICU	Intensive Care Unit
MRFF	Medical Research Future Fund
PET/CT	^{18}Fluoro-2-deoxy-D-glucose Positron Emission Tomography with Computed Tomography (^{18}F-FDG PET)
RAR	Response Adaptive Randomization
RCT	Randomized Controlled Trial
RSA	Region-Specific Appendix
SAB	*Staphylococcus aureus* bacteraemia
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SNAP	*Staphylococcus aureus* Network Adaptive Platform trial
SOC	Standard of Care

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) and Simulations Appendix (details of the current simulations of SNAP), 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 of 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 and Simulations Appendices. 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 Statistics Working Group 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 Appendix is listed in the Protocol Summary and on the study website (https://www.snaptrial.com.au).

3. PET/CT DOMAIN-SPECIFIC APPENDIX VERSION

The version of the PET/CT Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1.0: Approved by the PET/CT Domain-Specific Working Group (DSWG) on 24 March 2023

4. PET/CT DOMAIN GOVERNANCE

4.1. Domain members

Chairs: Anna Goodman
Mical Paul

Members: Steven Tong
Joshua Davis
Andrew Scott
Roslyn Francis
Gary Cook
George Heriot
Neta Petersiel
Nesrin Ghanem-Zoubi
Martin Llewelyn
Jennifer Bostock
Anna McGlothlin
Olga Kagana
Abby Douglas
Marjolein Hensgens

Jaap ten Oever

Ilse Kouijzer

4.2. Contact Details

Chairs: Dr Anna Goodman

MRC Clinical Trials Unit at University College London

London, WC1V 6LJ, UK

Phone +44 75 4815 3014

Email anna.goodman@ucl.ac.uk

Dr Mical Paul

Clinical Research Institute at Rambam

Hafia, 3109601, Israel

Phone +972 50 206 2140

Email paulm@technion.ac.il

Project Manager: SNAP Clinical Trial Manager

The Peter Doherty Institute for Infection and Immunity

792 Elizabeth St Melbourne VIC AUSTRALIA

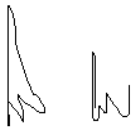
+61 (0) 38344 2554

snap-trial@unimelb.edu.au

5. PET/CT DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The PET/CT Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official PET/CT Domain-Specific Appendix for the SNAP trial.

Signed on behalf of the committee:

Chair Anna Goodman		Date	31 March 2023
Chair Mical Paul		Date	31 March 2023

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the SNAP trial to evaluate the effectiveness of FDG PET/CT imaging in patients with *Staphylococcus aureus* bacteraemia admitted to a participating hospital.

6.2. Domain-specific background

6.2.1. PET/CT background

Staphylococcus aureus bacteraemia (SAB) is associated with deep foci in 40–50% of cases, through local or haematogenous spread or seeding (1,2). Detecting infectious foci in SAB is a prerequisite to source control, which is critical to improving outcomes, e.g., through removal of implanted material, drainage, or surgery. However, in 15–20% of cases no focus can be found, and in others additional foci may be missed (1). When the foci are not found, this is associated with 50% higher mortality (1–3). Identification of deep foci is associated with a need for a longer treatment course, but recent trials have failed to improve survival by adjusting antibiotic therapy alone (4,5).

^{18}Fluoro-2-deoxy-D-glucose (F-FDG) Positron Emission Tomography (denoted 'PET') is widely used to stage cancer by detecting active cancer cells that metabolise glucose at a higher rate than normal tissues. PET can additionally detect foci of infection, as activated white cells also have a high glucose metabolism. PET, when combined with computed tomography (denoted 'PET/CT'), further allows anatomic information to be obtained. ^{18}F-FDG PET (referred to as 'PET/CT' throughout the remainder of the document) leads to radiation exposure equivalent to approximately 5.6 years of background radiation, well within safe limits. However, the role of these imaging modalities to rapidly detect deep infectious foci in SAB remains unclear. The European Medicines Agency (EMA) licensed FDG for use in

PET/CT investigation of bacteraemia on the basis of observational studies (6), but this weak evidence has translated into limited uptake in clinical practice.

Although previous studies in this area have been small and retrospective, they suggest there may be potential to improve health outcomes. A large randomised controlled trial (RCT) is needed to provide solid clinical evidence for future global implementation. The proposed study aims to improve SAB management using PET/CT through the mechanism of increased detection of foci of infection. The overall hypothesis is that optimal detection of infectious foci will improve clinical outcomes through comprehensive source control and tailored antibiotic management. This hypothesis is measured in the PET/CT domain secondary endpoints in additional to the primary endpoint of the arm which aligns to an overall trial aim and core trial secondary endpoints.

6.2.2. Evidence for efficacy of PET/CT

We conducted a literature search on 17/1/22 via PubMed using keywords '*Staphylococcus aureus*' AND 'positron emission tomography'. Eligible studies were RCTs, cohort and case-control studies where patients with SAB infections who underwent PET/CT were compared to control patients without PET/CT.

We identified 5 observational studies (7–11) (aggregate N = 880). There were no RCTs. Four studies found an association between performance of PET/CT (7–11) and lower mortality (Fig 1, risk difference of 7-24%), with the association retained on multivariable analysis adjusting for prognostic covariates in two of the studies (aOR 0.20 [95% CI 0.07–0.62](8) & 0.39 [95% CI 0.18–0.84](7), aOR were not reported or methods were unclear in the other two studies). A small study found an uncertain impact on mortality compared high risk 'cases' who did not have signs of metastatic infection on PET/CT and low risk 'controls'(10) , indicating that PET/CT might effectively re-stratify these previously high risk patients as lower risk.

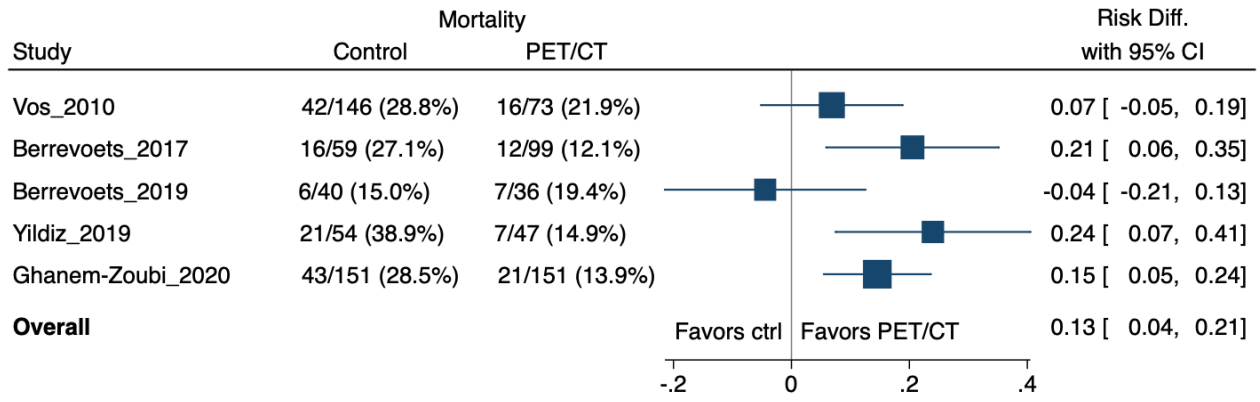


Figure 1: *Forest plot of studies comparing patients with SAB infections who received PET/CT (cases) and those without PET/CT (controls). The risk difference in 90-day mortality is represented. The combined risk difference is not provided due to heterogeneity of studies.*

One of the studies was a prospective case-control study (12), which found the mortality from SAB was 28% among the controls and 14% in those who underwent PET (21/151 [13.9%] vs 43/151 [28.5%], p = 0.002). There were differences between the control and cases: the cases were recruited prospectively (so would have had strong infectious diseases team input), whilst the controls were recruited retrospectively upon review of notes.

In the two studies clearly reporting on changes in management, 19/99 (19%) (8) and 27/151 (18%) (7) patients had a new drainage procedure, and 60/99 (61%) had a change in antibiotic duration(8).

Two studies reported a rate of new diagnostic findings related to SAB infections in the PET/CT group of 67% (7) and 74% (8) (control group not reported) and one study reported detecting more infective foci in those with PET/CT than controls (49 vs 13 foci, p<0.01)(11).

All these studies are subject to bias (evaluated using ROBINS-I tool), due to confounding, immortal time bias, selection of participants and selection of reported results (13). Therefore, while positive associations can be drawn, the GRADE quality of evidence is low.

Indeed, a recent observational cohort of patients with *S. aureus* bacteraemia in the Netherlands found that an initial adjusted hazard ratio (aHR) of 0.5 (95% confidence interval [CI] 0.34–0.74) for 90-day infection related mortality for those who underwent PET/CT compared to no PET/CT. After correction for immortal time bias, PET/CT no longer had a detectable effect on infection related mortality with an aHR of 1.00 (95% CI 0.77–2.21) (14).

6.2.3. Potential adverse effects of PET/CT

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 women or children less than 18 years of age, hence their exclusion from this domain. Women who are breastfeeding are also excluded. 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. The procedure requires an intravenous cannula and transporting to and from the

imaging department. This can be uncomfortable for an unwell patient and thus there is an exclusion of the clinically unstable patient.

6.2.4.Need for a clinical trial of PET/CT

Globally there are no previous published RCTs of enhanced imaging in SAB, but there is one trial currently recruiting. TEPSTAR (NCT03419221) is an ongoing RCT randomising 290 adults with SAB to PET/CT vs standard of care (expected recruitment completion January 2024, current number unknown) (15), where the primary outcome is the presence of at least one deep focus of infection. This trial therefore tests only whether routine imaging increases detection of foci (mechanism) but not whether this improves outcome (efficacy).

More accurate diagnosis of SAB infection foci may result in considerable improvements in management (better source control, tailoring of antibiotic duration) for a common high mortality disease (2–10 deaths per 100 000 per year (1,3)). A single patient with SAB infections often receives multiple imaging modalities, visiting the radiology department as many as 12 times during the index admission (16). Such multiple visits are inefficient, uncomfortable and may delay the delivery of effective treatment. Early enhanced imaging should improve patient experience by streamlining radiology visits. Although a single PET/CT is considered expensive relative to standard imaging, it may be cheaper than the total cost of multiple other scans. This will be assessed as a health economic analysis within SNAP-PET. More broadly, if found to be a beneficial intervention, the results may open the field for similar studies of PET/CT for other infectious diseases syndromes (e.g., other causes of sepsis).

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of PET/CT for patients with SAB requiring admission to hospital. The overall hypothesis is that optimal detection of infectious foci will improve clinical outcomes and reduce microbiological treatment failure through comprehensive source control and tailored antibiotic management. This hypothesis is measured in the PET/CT domain-specific secondary endpoints in additional to the primary endpoint of the arm which aligns to an overall trial aim and core protocol secondary endpoints.

The primary objective is to evaluate the impact of PET/CT on clinical outcomes including 90-day mortality and Desirability of Outcome Ranking (core secondary outcomes).

Secondary objectives are to determine the impact of PET/CT on clinical decision making, antibiotic use (duration and route), detection of infection foci, use of radiological investigations, and health economic costings.

The PET/CT findings may lead to better tailored management of SAB infections including improved use of source control procedures and more appropriate durations of antibiotic treatment. This may reduce mortality in SAB. We will also evaluate patient centred outcome measures that are already included as part of SNAP core outcomes.

We hypothesize that the probability of all-cause mortality at 90 days after enrolment will differ based on the PET/CT intervention. The following interventions will be available:

- Usual care with FDG PET/CT
- Usual care with no PET/CT

8. TRIAL DESIGN

This domain will be conducted as part of the SNAP trial (see Core Protocol Section 6). Treatment will be randomly allocated, as described in the Core Protocol Section 6.7.

8.1. Population

Patients with *S. aureus* bacteraemia who meet the eligibility criteria and are admitted to a participating hospital.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 6.5) AND all of the domain-level inclusion and none of the domain-level exclusion criteria. Patients eligible for SNAP may have conditions that exclude them from the PET/CT Domain.

All platform-eligible participants will be randomised within the PET/CT domain at platform entry (to PET/CT or no PET/CT) but the intervention allocation will remain hidden unless and until the participant is found to meet the eligibility criteria for the PET/CT domain.

Eligibility will be assessed at platform **Day 7** (+/- 2 days).

8.2.1. Domain inclusion criteria

- PET/CT participating site

- Patient is accessible for PET/CT – a patient is considered accessible if the site team are able to access the participant medical records, arrange for a PET/CT scan for the patient, and discuss this domain with the patient and their treating healthcare providers.

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they meet any of the following:

- Pregnant – patients of childbearing potential should be assessed for pregnancy status and a pregnancy test performed (if not performed within the past 10 days)
- Currently breastfeeding
- < 18 years of age
- Patient has had PET/CT in the past 7 days
- Patient needs PET/CT in the next 7 days (in the opinion of the clinical team, at the time of eligibility assessment)
- Clinically unstable for PET/CT (as judged by the treating clinical team, taking into account need for organ support (including inotropes) and capacity to lie flat for the PET/CT)
- Contraindication to PET/CT (e.g., claustrophobia, persistently elevated blood sugar levels [>12.5mmol/L] that cannot be corrected).
- Patient no longer willing to participate in the domain – in the days leading up to judging eligibility, it may be helpful to discuss with the patient the potential for PET/CT vs no PET/CT to allow imaging planning
- Clinician deems participation in this domain is not in the patient's best interests (provide reason)

8.2.3. Intervention exclusion criteria

Nil.

8.3. Interventions

8.3.1. PET/CT Interventions

- <u>Usual care with PET/CT</u>

  Whole body FDG PET/CT imaging will be performed using a standardised protocol describing patient preparation and minimum specifications for radiopharmaceutical production, quality control, and PET/CT acquisition.
    - For all participants there should be a minimum 6-hour fast prior to the PET/CT. Where there is clinical suspicion for cardiac related infections (endocarditis, presence of

prosthetic valves, cardiac implantable devices), there should be a 12-hour water-only fast prior to the PET/CT to suppress physiological FDG uptake in normal myocardium.

- Intravenous contrast for the CT is not required. The default will be for a non-contrast CT. If contrast is used, then the reading of the PET/CT should use non-contrast images. Further details are provided in the Imaging Manual.
- The logistics of PET/CT reporting will usually reflect local clinical practice. At a minimum this includes reporting using a standardized framework by a board-certified nuclear medicine physician or a board-certified radiologist experienced in reading PET/CT using recent reporting guidelines. Where available, the PET/CT images can be reviewed and reported centrally. There will be a PET/CT Imaging Manual that contains region specific details.
    - The results will be provided to the treating clinical team and local site investigators within 48 hours of the procedure.
    - Therefore, results from the PET/CT should be available to treating clinical team and local site investigators between platform days 7-16 (allowing 48 hours from performance of PET/CT between platform days 5-14).
- Any decisions on management following PET/CT results will be left to the clinical team and site investigators. Decisions should follow local guidelines; some guidance is provided below and in the RSAs. These are not meant to be prescriptive and management decisions that differ from the below are not considered protocol deviations.
    1. **Large, undrained infection foci** which are amenable to open or percutaneous drainage should be considered for an appropriate source control procedure.
        a) If the patient had been randomised to oral switch in the Early Oral Switch (EOS) domain, it may be justified to switch back to intravenous antibiotic therapy until adequate source control has occurred. Such participants should then be switched back to the allocated oral therapy.
    2. For patients with **uncomplicated (low risk)** SAB infection (as defined in the core protocol):
        a) If no new foci are found – suggested total antibiotic treatment duration to be 2 weeks

b) If new foci are found – consider source control procedure and consider extending treatment duration to ≥4 weeks. However, small clinically inapparent foci may not require longer durations.

3. For patients with **complicated (high risk)** SAB infection (as defined in the core protocol):
    a) If no deep- seated foci are found – suggested total antibiotic duration to be 4 weeks, but can consider ceasing after 2 weeks
    b) If underlying prosthesis (includes prosthetic cardiac valve, vascular grafts, joint prosthesis) not infected – suggested total antibiotic duration to be 4 weeks, but can consider ceasing after 2 weeks
    c) If endovascular (e.g., endocarditis, vascular graft infection) foci are found – suggested total antibiotic duration to be ≥6 weeks
    d) If infection of extravascular prosthetic material (e.g., joint prosthesis) are found – suggested total antibiotic duration to be ≥6 weeks
    e) If appropriate source control has occurred or does occur (e.g., infected prosthesis removed, septic joint adequately washed out) – suggested total antibiotic duration shorter than the above recommendations may be considered

- Usual care with no PET/CT.

  No PET/CT will be recommended. However, treating clinical teams can investigate as per usual care with clinical follow-up and other imaging modalities. Although PET/CT cannot ethically be forbidden, costs will not be covered by the trial if the treating clinical team deems it necessary for best medical care (data on crossovers will be collected). To mitigate the likelihood of PET/CT taking place in this arm, sites where PET/CT is common in practice may not be selected for participation in this domain, as it may result in a large proportion of the control arm receiving PET/CT.

  Overall management of SAB infection will follow SAB infection management guidelines (some guidance is provided in the RSAs) and adherence to allocated treatments in the other SNAP domains.

8.3.2.Considerations for other domains

- Early Oral Switch Domain – participants should aim to continue on oral antibiotics or intravenous antibiotics as allocated, regardless of PET/CT findings. For example, if a patient is deemed eligible for the early oral switch domain at platform day 7 (and thus is determined to have low risk disease at that time), and PET/CT subsequently demonstrates additional

metastatic foci, the route of antibiotic therapy (IV or oral) should ideally remain as allocated. The clinical team may choose to extend the duration of therapy. If the participant needs to fast for an operative procedure, then oral therapy may be substituted for intravenous therapy until the patient can re-start oral therapy.

8.3.3. Timing of initiation of PET/CT domain

Participants enrolled in SNAP are randomised within the PET/CT domain at platform entry, but the reveal of allocation (usual care with PET/CT versus usual care with no PET/CT) only occurs once eligibility for the PET/CT domain is confirmed (see Section 9.4.1, Blinding).

Participants enrolled in SNAP will be assessed at platform Day 7 (+/- 2 days) for eligibility for the PET/CT domain. If the participant is eligible, reveal of allocation will occur. Participants will receive a PET/CT scan or not, according to allocation.

If the participant is allocated to receive a PET/CT scan:

- The nuclear medicine imaging centre for that site will be notified and a booking made for a SNAP-related PET/CT.

  For some trial sites, it may be possible to book a PET/CT time slot prior to the eligibility assessment, and for the procedure to be completed if allocated to PET/CT or the procedural slot relinquished if allocated to no PET/CT.
- The nuclear medicine imaging centre will then liaise with the research team and the treating clinical team to facilitate the performance of the PET/CT ideally within the window of platform Day 7-12 ($\pm$ 2)

If the participant is not eligible at Day 7 ($\pm$ 2 days), then treatment is continued according to the treating clinician's discretion and there are no further assessments for eligibility. The allocation of domain intervention is never revealed for these participants.

8.4. Concomitant care

Participants will continue to receive all other routine clinical care, as described in the SNAP core protocol. In the event that additional diagnostic imaging is required for a new or worsening infection, this will be at the discretion of the treating clinical team and will not constitute a protocol deviation. Concomitant imaging will be documented.

8.5. Endpoints

8.5.1.Primary endpoint

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

8.5.2.Secondary endpoints

All secondary platform endpoints as specified in the Core Protocol Section 6.8 apply to the PET/CT domain. Of particular note to this domain are core secondary endpoints 6 (microbiological treatment failure between day 14 and day 90 from platform entry) and 7 (diagnosis of new infection foci between day 14 and day 90 from platform entry), 14 and 15 (antibiotic endpoints).

The domain-specific secondary endpoints are:

1. Change in proposed management of *S. aureus* bacteraemia following PET/CT results, comparing proposed management at domain entry and proposed management following receipt of PET/CT results (this outcome is relevant to PET/CT arm only). This is a key secondary end-point and published analyses may be based on this key secondary outcome.

   The treating clinical team will complete standardised forms detailing the proposed management plan with regards to investigations, source control procedures, antibiotic route (oral or intravenous), and antibiotic duration, at two time points:

   1) Pre-Reveal Proposed Management Plan at platform **Day 7** ($\pm$ 2 days) – once patient confirmed eligible for the domain but prior to allocation reveal, and then at
   2) Post-PET Proposed Management Plan at platform **Day 14** (-7, +2 days) – ideally within 48 hours of receiving the PET/CT report.

   These two proposed plans will be compared. This endpoint captures the direct impact of the PET/CT report on proposed management plans.

   The number of changes will be classified as 0, 1, 2, 3, 4 (according to number of management categories changed – antibiotic route, antibiotic duration, investigations, source control procedures). Changes will also be classified as: *None, Low* (only a change in 1 of investigations or antibiotic route), or *High* (change in any of source control procedures, antibiotic duration, or [investigations AND antibiotic route]). The methodology in assessing change in proposed management is informed by methods used in cancer studies conducted by CI Scott and Francis (17).

2. Change in management of *S. aureus* bacteraemia, comparing proposed management at domain entry and actual management (this outcome is relevant to both PET/CT and no PET/CT arms).

   The treating clinical team will complete forms detailing the proposed management plan and actual management with regards to investigations, source control procedures, antibiotic route (oral or intravenous), and antibiotic duration, at two time points:

   1) Pre-Reveal Proposed Management Plan at platform **Day 7** ($\pm$ 2 days) – once patient confirmed eligible for the domain but prior to allocation reveal
   2) Actual management at **Acute & Total Discharge** – collecting management from domain entry to total hospital discharge.

   Note that the pre-reveal proposed management plan is the same as that for the domain-specific secondary endpoint 1 above.

   The proposed and actual management will be compared. This endpoint captures whether the PET/CT report has actually impacted patient management and would be considered a more patient centric endpoint.

   The number of changes will be classified as 0, 1, 2, 3, 4 (according to number of management categories changed – antibiotic route, antibiotic duration, investigations, source control procedures). Changes will also be classified as: *None, Low* (only a change in 1 of investigations or antibiotic route), or *High* (change in any of source control procedures, antibiotic duration, or [investigations AND antibiotic route]). The methodology in assessing change in proposed management is informed by methods used in cancer studies conducted by CI Scott and Francis (19).

3. Diagnosis of new infection foci between domain entry and platform day 14. We would expect that more new infection foci will be diagnosed at this early stage in the PET/CT group. New foci are defined as those not previously recognised on clinical grounds or existing imaging or other diagnostic procedures. The site and number of sites of new foci will be determined.
4. Total imaging investigations between domain entry and total hospital discharge. Data on all imaging investigations performed will be collected. We expect that the earlier diagnosis and management of infective foci may result in fewer additional imaging procedures being required. The type and number of imaging investigations will be collected.
5. Estimated total radiation exposure between domain entry and total hospital discharge. Data on all radiological imaging performed will be collected. Although PET/CT involves radiation exposure (equivalent to approximately 5.6 years of background radiation), the earlier

diagnosis and management of infective foci may result in fewer additional imaging procedures being required.

Average radiation exposure estimates will be generated at a central level for the most common radiological procedures and used as the radiation exposure for each relevant procedure performed.

6. Total diagnostic and source control procedures between domain entry and total hospital discharge. Includes procedures requiring local or general anaesthetic, concurrent radiological imaging, percutaneous procedures, removal of devices, prostheses, other foreign material, drainage of abscesses and collections. The type and number of procedures will be collected.
7. Detailed health economic cost analysis. In addition to the health economic analysis specified in the core protocol, the PET/CT domain will collect additional information regarding imaging procedures (including PET/CT) and source control procedures. We will also collect EQ-5D-5L quality of life scores at domain entry and platform day 90. Further details of the health economic cost analysis are found in the Health Economic Appendix.
8. Total incidental diagnoses made via any imaging investigations, including PET/CT, from domain entry to total hospital discharge. Data on any new, previously unknown diagnoses that are unrelated to SAB, made via any imaging investigations performed during total hospitalisation will be collected. The type and number of new diagnoses will be collected.
9. Serious Adverse Events (SAEs) that occur as a consequence of any imaging investigation or radiology procedure undertaken from domain entry to total hospital discharge. Serious Adverse Reactions (SARs) will be collected as per the core protocol for the PET/CT intervention. Serious Adverse Reactions (SARs) should be captured in all participants in this domain irrespective of intervention allocation. These are Serious Adverse Events (SAEs) that occur as a consequence of any imaging investigation or radiology procedure including PET/CT, undertaken from domain entry to total hospital discharge. This includes SAEs that are unrelated to SAB but that are possibly, probably or definitely attributable to an imaging investigation or radiology procedure.

9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Microbiology

No specific additional microbiological testing will be performed, or additional microbiological data collected for this domain.

9.1.2. Clinical data and sample collection

Additional domain-specific data will be collected:

- Eligibility screening completed at platform Day 7 ± 2 for all participants enrolled in the platform at participating PET/CT sites.
- Data to determine high risk or low risk SAB status noted for all participants at time of domain eligibility assessment.
- Proposed management at platform Day 7 (± 2 days), prior to the reveal of PET/CT domain assignment (all participants in the PET/CT domain)
- Proposed management plan at platform Day 14 (-7, +2 days), but ideally within 48 hours of receiving the PET/CT report (only for participants in the PET/CT arm)
- New infection foci between domain entry and platform day 14
- Actual management recorded at acute discharge and at total discharge, collecting management between domain entry and total hospital discharge, including imaging investigations and diagnostic and source control procedures performed
- Incidental diagnoses made via any imaging investigations between domain entry to total discharge
- Serious Adverse Events (SAEs) that occur as a consequence of any imaging procedure or radiological investigation
- EQ-5D-5L at domain entry and at platform day 90.

9.1.3. Domain-specific study timeline

Table 1: Domain-specific schedule of visits, data collection and follow-up.

Visit Day	**Day 1**	**Day 7 (±2)**	**Day 7-12 (±2)**	**Day 14**	**Acute D/C**	**Total D/C**	**Day 90**
Consent	X						
Eligibility assessment for PET/CT		X					

Visit Day	Day 1	Day 7 (±2)	Day 7-12 (±2)	Day 14	Acute D/C	Total D/C	Day 90
Collect high/low risk SAB status		X					
Pre-reveal proposed management plan		X[1]					
Allocation reveal, if eligible		X					
FDG PET/CT[2]			X[3]				
Release of PET/CT report[2]			X[4]				
Post-PET proposed management plan[2]				X[5]			
Data on PET/CT results				X			
Data on PET/CT protocol adherence				X		X[6]	
Data on new infection foci[7]				X			
Actual management[8]					X	X	
Data on incidental diagnoses[8]					X	X	
EQ-5D-5L		X					X
Collect SAEs related to imaging procedures / radiological investigations		X	X	X	X	X	

[1] Completed once patient assessed as eligible for the domain, and prior to the reveal of PET/CT allocation

[2] Only for participants in the PET/CT arm

[3] PET/CT should ideally be performed within 48 hours of allocation to PET/CT arm

[4] PET/CT results and report should ideally be provided within 48 hours of PET/CT performance

[5] Completed on Day 14 (-7, +2), ideally within 48 hours of receiving the PET/CT report

[6] Only for participants in the no PET/CT arm

[7]Collected for the period between domain entry and Day 14

[8] Collected for the period between domain entry and total discharge

9.1.4. Domain-specific study visit day details

All core study visit details are specified in the Core Protocol (Section 8.8). Additional domain-specific study procedures are outlined below.

9.1.4.1. Day 1

In addition to the procedures outlined in the Core Protocol (Section 8.8), the following additional domain-specific procedures will be required for all participants at PET/CT participating sites.

- Obtain consent for PET/CT domain

9.1.4.2. Day 7 (+/- 2)

In addition to the procedures outlined in the Core Protocol (Section 8.8), additional domain-specific screening procedures will occur as per the eligibility criteria outlined in Section 8.2. This will include checking that the patient still agrees to participate in this domain.

Additional domain-specific activities will include:

- Collect data to determine high risk or low risk SAB status, as defined in the core protocol
- Collect pre-reveal proposed management plan for all participants in the PET/CT domain
- Collect EQ-5D-5L quality of life score
- Reveal PET/CT domain allocation
- Review safety events that occur as a consequence of any imaging investigation or radiology procedure

9.1.4.3. Day 7-12 (+/- 2)

In addition to the activities outlined in the Core Protocol (Section 8.8), additional domain-specific procedures will occur.

Additional domain-specific activities will include:

- Perform PET/CT, ideally within 48 hours of allocation to PET/CT arm
- Release of PET/CT report to treating clinician team and site investigators, ideally within 48 hours of PET/CT performance
- Review safety events that occur as a consequence of any imaging investigation or radiology procedure

9.1.4.4. Day 14

In addition to the activities outlined in the Core Protocol (Section 8.8), additional domain-specific procedures will occur.

Additional domain-specific activities will include:

- Collect post-PET proposed management plan on Day 14 (-7, +2), ideally within 48 hours of receipt of PET/CT report, if randomised to PET/CT arm
- Collect data on PET/CT results
- Collect data on PET/CT protocol adherence (for participants allocated to the PET/CT arm)
- Collect data on new infection foci diagnosed between domain entry and platform day 14

- Review safety events that occur as a consequence of any imaging investigation or radiology procedure

9.1.4.5. Acute Hospital Discharge

Core activities from Day 2 until acute hospital discharge are outlined in the Core Protocol (Section 8.8).

Additional domain-specific activities will include:

- Collect data on actual management, between domain entry and acute discharge, including imaging investigations and diagnostic and source control procedures performed
- Collect data on incidental diagnoses made between domain entry to acute discharge
- Review safety events that occur as a consequence of any imaging investigation or radiology procedure

9.1.4.6. Total Hospital Discharge

Core activities from Day 2 until total hospital discharge are outlined in the Core Protocol (Section 8.8).

Additional domain-specific activities will include:

- Collect data on PET/CT protocol adherence (for participants randomised to the no PET/CT arm)
- Collect data on actual management, between acute discharge and total hospital discharge, including imaging investigations and diagnostic and source control procedures performed
- Collect data on incidental diagnoses made between acute discharge and total hospital discharge
- Review safety events that occur as a consequence of any imaging investigation or radiology procedure

9.1.4.7. Day 90

In addition to the activities outlined in the Core Protocol (Section 8.8), additional domain-specific procedures will occur.

Additional domain-specific activities will include:

- Collect EQ-5D-5L Quality of Life score

9.2. Protocol deviations specific to this domain

Protocol deviations should be reported as defined in the Core Protocol (Section 8.13.2).

Domain-specific protocol deviations will be documented and reported in the eCRF for this domain, as specified in the Breach Reporting SOP.

9.3. Criteria for discontinuation

Refer to Core Protocol Section 8.10 for criteria for discontinuation of participation in the SNAP trial.

9.4. Blinding

9.4.1. Blinding

At platform entry, participants will be randomised to usual care with FDG PET/CT or usual care with no PET/CT strategies. Investigators and participants will remain blinded to the allocation until the participant is judged to be eligible at platform **Day 7 ± 2**. Once a participant is eligible, the allocation will be revealed, and the investigator and participant will be unblinded.

Trial investigators, site and study personnel will remain blinded to pooled domain outcomes and summaries that are aggregated by intervention until the completion of the domain.

9.4.2. Unblinding

Unblinding is not relevant at the individual participant and site investigator level as once eligibility is reached, the allocation is not blinded.

10. STATISTICAL CONSIDERATIONS

10.1 Estimands, endpoints, and intercurrent events

10.1.1 Primary estimand

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

10.1.2 Secondary estimands

All core secondary estimands, endpoints, and intercurrent events strategies are specified in the Statistical Analysis Appendix.

The domain-specific secondary estimands, endpoints, and intercurrent events are defined as follows:

Table 2: Estimand calculations

Estimand/Objective/Target population	Endpoint/Population-level summaries	Intercurrent events strategy
Estimand D.1 To evaluate, within the PET/CT domain, the effect of revealed PET/CT intervention on the proposed management of *S. aureus* bacteraemia, in domain eligible participants who have been allocated to PET/CT.	Endpoint: Change in proposed management of S. aureus bacteraemia comparing prior to allocation to PET/CT and following PET/CT results, classified as 0, 1, 2, 3, 4 (according to number of management categories changed – antibiotic route, antibiotic duration, investigations, source control procedures). Changes will also be classified as: None, Low (only a change in 1 of investigations or antibiotic route), or High (change in any of source control procedures, antibiotic duration, or [investigations AND antibiotic route]). Population summary: Log-cumulative odds ratio assuming proportional odds between the intervention and control groups.	Principal stratum policy (per protocol principle): those allocated to PET/CT and received PET/CT by platform day 14
Estimand D.2 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention on the actual management of *S. aureus* bacteraemia, in domain eligible participants.	Endpoint: Change in management of S. aureus bacteraemia, comparing proposed management at domain entry and actual management by total hospital discharge. Changes are classified as 0, 1, 2, 3, 4 (according to number of management categories changed – antibiotic route, antibiotic duration, investigations, source control procedures). Changes will also be classified as: None, Low (only a change in 1 of investigations or antibiotic route), or High (change in any of source control procedures, antibiotic duration, or [investigations AND antibiotic route]). Population summary: As for estimand D.1.	Treatment policy strategy (intent-to-treat principle)

Estimand D.3 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention, on the probability of a diagnosis of new infection foci between domain entry and total hospital discharge in domain eligible participants	Endpoint: Diagnosis of new infection foci between domain entry platform day 14. Population summary: Log-odds ratio of the stated event between intervention and control groups.	Treatment policy strategy (intent-to-treat principle)
Estimand D.4 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention, on the number of imaging investigations between domain entry and total hospital discharge in domain eligible participants	Endpoint: Total imaging investigations between domain entry and total hospital discharge Population summary: Difference in the log-expected count between the intervention and control group.	Treatment policy strategy (intent-to-treat principle)
Estimand D.5 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention, on the total radiation exposure between domain entry and total hospital discharge in domain eligible participants	Endpoint: Estimated total radiation exposure between domain entry and total hospital discharge. Population summary: Difference of means in total radiation exposure between intervention and control group	Treatment policy strategy (intent-to-treat principle)
Estimand D.6 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention, on the total number of diagnostic and source control procedures between domain entry and total hospital discharge in domain eligible participants	Endpoint: Total diagnostic and source control procedures between domain entry and total hospital discharge. Population summary: As for estimand D.4.	Treatment policy strategy (intent-to-treat principle)
Estimand D.7 To evaluate, within the PET/CT domain, the effect of revealed randomised intervention, on the total number of incidental diagnoses made between domain entry and total hospital discharge in domain eligible participants	Endpoint: Total incidental diagnoses made via any imaging investigations, including PET/CT, from domain entry to total hospital discharge. Population summary: As for estimand D.4.	Treatment policy strategy (intent-to-treat principle)
Estimand D.8 To evaluate, within the PET/CT domain, the effect of revealed	Endpoint: Serious Adverse Events (SAEs) that occur as a consequence of any imaging	Treatment policy strategy (intent-to-treat principle)

randomised intervention, on the total number of Serious Adverse Events (SAEs) that occur as a consequence of any imaging investigation or radiology procedure between domain entry and total hospital discharge in domain eligible participants	investigation or radiology procedure undertaken from domain entry to total hospital discharge. Population summary: As for estimands D.4.	

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

10.2 Statistical modelling

10.2.1 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.

10.2.2 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.

The domain-specific endpoints D.1 and D.2 described in Section 10.1 are ordinal and have log-cumulative odds ratios that will be modelled using Bayesian cumulative logit models assuming proportional odds. The domain-specific endpoint D.3 is binary and have log-odds population summaries that will be modelled using a Bayesian binomial model with a logit link. The domain-specific endpoints D.4, D.6, D.7, and D.8 are count data, and will be modelled using a Bayesian negative binomial model. The domain-specific endpoints D.5 is continuous and, after any necessary transformations, will be modelled using a Bayesian linear model with normally distributed errors. See the Statistical Analysis Appendix.

10.3 Decision criteria

Stopping decisions in this cell are based on whether the posterior probabilities that the intervention is **superior,** with respect to the cell control, is above, or below, a pre-specified threshold. Where a cell stopping decision is recommended because a posterior probability is below the pre-specified threshold, we say that it is futile to continue with the objective of demonstrating superiority.

The primary objective for this domain is to determine if PET/CT is superior to no PET/CT. Superiority is defined as an OR < 1 for the primary endpoint (where an OR > 1 indicates an increase in mortality for PET/CT compared to no PET/CT).

As there are constraints on the total sample size achievable in this domain of approximately 820 participants, no scheduled analyses are planned prior to the final analysis when 820 participants are reached. In all other respects the decision criteria for this appendix are those outlined in the Core Protocol (Section 9.12) and the Statistical Appendix.

10.4 Randomisation

Participants will be randomised at platform entry in a fixed 1:1 ratio. A patient's allocated intervention will be revealed at the time that domain eligibility criteria are confirmed. Response adaptive randomization may be applied if additional interventions within this domain are included.

10.5 Interactions with domains

An *a priori* interaction with the early oral switch domain is considered possible and will be incorporated into the statistical models used to analyse this domain. Allocation to oral antibiotics or continued intravenous antibiotics may influence management decisions following the PET/CT.

An *a priori* interaction with other domains (backbone antibiotic and adjunctive antibiotic) are not considered likely and will not be incorporated into the statistical models used to analyse this domain.

10.6 Pre-specified secondary analyses

Pre-specified secondary analyses on the primary estimand will be performed by modifying the primary statistical model to include the following covariates and their treatment interactions:

1. <u>Low risk vs high risk bacteraemia (as defined at time of eligibility assessment for domain entry)</u>

   It might be expected that any effect of PET/CT would most benefit complicated bacteraemia where additional infection foci may be more likely, and thus any findings would influence subsequent management decisions. However, a prospective study of PET/CT as an intervention found greater benefit in low risk bacteraemia (12).

   High risk bacteraemia is defined in the SNAP Core protocol (AKA as complicated bacteraemia) as patients with one or more of the following:

   i. An implanted intravascular prosthesis or endovascular device
   ii. Day 2 (from platform entry) blood cultures positive
   iii. Fever (any temperature 37.8 C or above on platform day 2)
   iv. Evidence of deep seated (i.e., not just line related or skin and soft tissue related) or metastatic infection. This includes evidence of endocarditis.

   For the purpose of the PET/CT domain, the determination of baseline low risk vs high risk bacteraemia will occur at the time of eligibility assessment (noting that this may be different from the final determination of uncomplicated vs complicated bacteraemia)

2. Primary bloodstream infection (i.e., unknown focus of infection at the time of domain eligibility assessment) versus other (i.e., any known focus of infection at the time of domain eligibility assessment).

   Those with a primary bloodstream infection may have a poorer prognosis and a vascular focus of infection, and these patients may derive a greater benefit from PET/CT than those with a known focus

3. Nosocomial (index blood culture collected >48 hours after hospital admission) vs community onset bloodstream infection.

   Those with a community onset bloodstream infection are more likely to have complicated bacteraemia and/or an unknown focus, therefore may have worse outcomes. PET/CT may have greater value in these patients compared to those with nosocomial bacteraemia.

10.7 Principal stratum policy

The principal stratum policy (also known as a 'per protocol principle') for Estimand D1 uses the population as described in the following subsections.

10.7.1 If allocated to PET/CT

Underwent PET/CT by the end of platform day 14.

10.7.2 If allocated to no PET/CT

Did not undergo PET/CT by the end of platform day 21.

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Committee

The statistical analyses will evaluate superiority and futility for superiority, with pre-specified stopping rules. The DSMC should be aware of the pre-specified decision criteria for superiority and futility of PET/CT and may consider recommending stopping or changing aspects of the protocol if harm is demonstrated in the incidence of serious adverse reactions and for the secondary outcomes.

11.2. Potential domain-specific adverse events

Serious adverse reactions (SARs) should be captured in all participants in this domain irrespective of intervention allocation. These are serious Adverse Events (SAEs) that occur as a consequence of any imaging investigation or radiology procedure including PET/CT, undertaken from domain entry to total

hospital discharge. This includes SAEs that are unrelated to SAB but that are possibly, probably or definitely attributable to an imaging investigation or radiology procedure.

11.3. Domain-specific consent issues

Consent for the PET/CT domain will be taken at platform entry, along with consent for the platform and other domains. Patient agreement to participate in this domain will be re-confirmed at the time of eligibility assessment for this domain at platform Day 7 $\pm$ 2, and re-confirmation of consent will be recorded in the database. If the patient no longer agrees to participate in the PET/CT domain, he/she will not be considered eligible at that time point.

Participants will be made aware that randomisation to receive a PET/CT within the PET/CT domain will not necessarily result in them staying in hospital for this treatment at sites where PET/CT scans are available to patients who have been discharged.

12.GOVERNANCE ISSUES

12.1. Authorship policy

Refer to SNAP Publications Policy for background and criteria for defining authorship for the SNAP Trial.

In addition to author and contributor positions noted in the Publications Policy document, the primary results manuscripts should offer authorship to representatives from the nuclear medicine imaging departments (two if the trial site has contributed at least one participant in the analysis dataset, three if 10 participants, four if ≥20 participants).

Representatives from the nuclear medicine imaging departments at trial sites are considered members of the site study teams. Other representatives from the nuclear medicine imaging departments may be listed as contributors.

12.2. Imaging Repository

All PET/CT images will be uploaded to a central repository and stored indefinitely in a de-identified manner using a unique study code. The central repository, and associated storage procedures and governance requirements, may vary by region and will be documented in the SNAP RSAs. The Participant Information and Consent Forms (PICFs) will include additional information and request additional consent for the images to be used for future related research.

12.3. Funding of domain

Funding sources for the SNAP trial are specified in the Core Protocol Section 2.5. This domain has received additional funding from MRFF International Clinical Trial Collaborations for 5 years to cover the operation of the PET/CT domain (and international as applicable).

12.4. Funding of domain interventions and outcome measures

Alliance Medial is supporting the provision of PET/CT scans in the United Kingdom.

12.5. Domain-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.

13.REFERENCES

1. Nambiar K, Seifert H, Rieg S, Kern W v., Scarborough M, Gordon NC, et al. Survival following Staphylococcus aureus bloodstream infection: A prospective multinational cohort study assessing the impact of place of care. Journal of Infection. 2018;77(6).

2. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in staphylococcus aureus bacteremia. Vol. 25, Clinical Microbiology Reviews. 2012.

3. Kaasch AJ, Barlow G, Edgeworth JD, Fowler VG, Hellmich M, Hopkins S, et al. Staphylococcus aureus bloodstream infection: A pooled analysis of five prospective, observational studies. Journal of Infection. 2014;68(3).

4. Thwaites GE, Scarborough M, Szubert A, Nsutebu E, Tilley R, Greig J, et al. Adjunctive rifampicin for Staphylococcus aureus bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. The Lancet. 2018;391(10121).

5. Davis J, Foo H, Lye D, Nelson J, O'Sullivan M, Paterson D, et al. Combination antibiotic therapy for methicillin-resistant Staphylococcus aureus bacteraemia: the CAMERA2 randomised controlled trial. In: 29th ECCMID. 2019.

6. Core summary of product characteristics (SmPC) and package leaflet for fludeoxyglucose (18F). European Medicines Agency. 2012.

7. Ghanem-Zoubi N, Kagna O, Abu-Elhija J, Mustafa-Hellou M, Qasum M, Keidar Z, et al. Integration of FDG-PET/CT in the Diagnostic Workup for Staphylococcus aureus Bacteremia: A Prospective Interventional Matched-cohort Study. Clinical Infectious Diseases. 2021;73(11).

8. Berrevoets MAH, Kouijzer IJE, Aarntzen EHJG, Janssen MJR, de Geus-Oei LF, Wertheim HFL, et al. 18F-FDG PET/CT Optimizes Treatment in Staphylococcus Aureus Bacteremia and Is Associated with Reduced Mortality. Journal of Nuclear Medicine. 2017 Sep;58(9):1504–10.

9. Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PFM, van Dijk APJ, Cuijpers MLH, et al. 18F-FDG PET/CT for detection of metastatic infection in gram-positive bacteremia. Journal of Nuclear Medicine. 2010 Aug;51(8):1234–40.

10. Berrevoets MAH, Kouijzer IJE, Slieker K, Aarntzen EHJG, Kullberg BJ, Oever J ten, et al. 18 F-FDG PET/CT-Guided Treatment Duration in Patients with High-Risk Staphylococcus

Aureus Bacteremia: A Proof of Principle. Journal of Nuclear Medicine. 2019 Jul;60(7):998–1002.

11. Yildiz H, Reychler G, Rodriguez-Villalobos H, Orioli L, D'Abadie P, Vandeleene B, et al. Mortality in patients with high risk Staphylococcus aureus bacteremia undergoing or not PET-CT: A single center experience. Journal of Infection and Chemotherapy. 2019 Nov;25(11):880–5.

12. Ghanem-Zoubi N, Kagna O, Abu-Elhija J, Mustafa-Hellou M, Qasum M, Keidar Z, et al. Integration of FDG-PET/CT in the Diagnostic Workup for Staphylococcus aureus Bacteremia: A Prospective Interventional Matched-cohort Study. Clinical Infectious Diseases. 2021;73(11).

13. Buis DTP, Sieswerda E, Kouijzer IJE, Huynh WY, Burchell GL, Berrevoets MAH, et al. [18F]FDG-PET/CT in Staphylococcus aureus bacteremia: a systematic review. BMC Infect Dis. 2022 Dec 24;22(1):282.

14. van der Vaart TW, Prins JM, van Werkhoven CH, Ten Doesschate T, Soetekouw R, van Twillert G, et al. Positive impact of [18F]FDG-PET/CT on mortality in patients with Staphylococcus aureus bacteremia explained by immortal time bias. Clin Infect Dis. 2023 Mar 4;

15. le Moing V. NCT03419221. France;

16. Brøndserud MB, Pedersen C, Rosenvinge FS, Høilund-Carlsen PF, Hess S. Clinical value of FDG-PET/CT in bacteremia of unknown origin with catalase-negative gram-positive cocci or Staphylococcus aureus. Eur J Nucl Med Mol Imaging. 2019;46(6).

17. Roach PJ, Francis R, Emmett L, Hsiao E, Kneebone A, Hruby G, et al. The Impact of ^{68}Ga-PSMA PET/CT on Management Intent in Prostate Cancer: Results of an Australian Prospective Multicenter Study. Journal of Nuclear Medicine. 2018 Jan;59(1):82–8.