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Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Submission date
03/12/2022

Recruitment status
Recruiting

Registration date
05/09/2023

Overall study status
Ongoing

Last Edited
04/10/2023

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Bacteraemia is a dangerous condition occurring when bacteria enter someone's blood (infection in the blood). Bacteria called Staphylococcus aureus (S. aureus) can cause S. aureus bacteraemia (SAB). Up to a third of people with SAB die within 3 months, even when treated with antibiotics. The aim of the research is to find out which treatments for this illness are best and if we can reduce the number of deaths from this disease.
The sort of questions we want to answer are:
1. What is the best main antibiotic treatment for S. aureus bacteraemia? This is being explored in a part of the trial (domain) called the 'backbone' (or main) antibiotic.
2. Would it be better to add an extra antibiotic to treat the condition? This domain is called Adjunctive (additional) antibiotic(s).
3. Once patients are feeling better do we need to continue antibiotics via a drip (usually in hospital) or could we give patients tablet antibiotics to take at home instead? This domain is called 'early oral switch' where some people are moved to tablet antibiotic(s) early.

Who can participate?
Patients infected with Staphylococcus aureus.

What does the study involve?
To work out which medicine is best researchers use clinical trials called a randomised controlled trial (RCT). The treatments are chosen randomly (like the flip of a coin) and one person may receive more than one treatment. Some patients then receive one or more medicines, whilst other patients receive different treatment(s). This means the same patient can be in more than one part of the trial. In this trial the drugs used are already licensed drugs used around the world to treat patients with this disease.

This is an international adaptive study so the researchers analyse the results as the study goes on rather than just at the end. If the results show any of the treatments do not work as well as others, they will be removed from the study. Similarly, new arms may be added. The initial length of the trial is 4 and a half years. Each person would be in the trial for 3 months with their data collected & stored longer.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
This trial is considered to be relatively low risk due to the fact that all of the interventions are already known treatments for S. aureus infections. No matter what arm participants are randomised to, they will be receiving treatments that are already licensed in the UK and known to be efficacious.
However, as with any medications, there are still risks, and there are a number of possible side effects in particular relation to antibiotic treatment. The PIS highlights that while risks are low with already licensed medications, these can still occur and outline some of the likely side effects. Where the combination of antibiotics may increase particular risks, this is highlighted in the PIS, and details are provided on the additional monitoring that will be undertaken as a result.
Data privacy poses another potential risk, however, this will be kept to a minimum through use of a secure database with tightly regulated access. Participant data will be pseudonymised before being entered into the study database, and this will only be viewable by the study site and the central trial and data managers. Any directly identifiable data will be restricted to the study site team, and to monitors to facilitate data checks.
Due to the severity of SAB, consent by the participant's authorised representative could also be a risk. In this situation the patient may have been consented to a study that they might not have consented to themselves. All patients will be approached to give their own consent as soon as feasibly possible in their recovery, and may withdraw their participation if they choose at any time in the trial.

Where is the study run from?
Medical Research Council Clinical Trials Unit, University College London (UK)

When is the study starting and how long is it expected to run for?
November 2022 to December 2029

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
Dr SNAP Study team

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-001238-13

Integrated Research Application System (IRAS)
1005342

ClinicalTrials.gov (NCT)
NCT05137119

Protocol serial number
CT19029, IRAS 1005342, CPMS 58551

Study information

Scientific Title
Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Acronym
SNAP

Study objectives
The objective of SNAP is to identify the effect of a range of clinical interventions on all-cause 90-day mortality in patients with SAB

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 30/08/2023, London – Hampstead Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8248; hampstead.rec@hra.nhs.uk), ref: 23/LO/0033

Study design
Interventional randomized controlled adaptive platform trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Staphylococcus aureus bacteraemia

Interventions

SNAP is a multicentre, pragmatic, multi-arm, open-label adaptive platform trial which aims to identify the effects of a range of clinical interventions on patients with Staphylococcus aureus Bacteraemia (SAB) in order to improve clinical outcomes. Participants will be randomly assigned to 1 arm within each domain for which they are eligible using a web-based module.

Currently available domains:
- Adjunctive Treatment Domain:
If the participant is deemed eligible they will be randomised to receive either:
1. Usual care plus clindamycin (5 days) - Intravenous clindamycin (or lincomycin) 600 mg every 8 h for 5 days.
2. Usual care alone

- Antibiotic Backbone Domain:
If the participant is deemed eligible they will be randomised within silos based on the antimicrobial susceptibility.
For PSSA, they will be randomised to:
1. Benzylpenicillin - Intravenous benzylpenicillin 1.8 g (3 million units) every 4 or 6 h. The minimum protocol duration of allocated study treatment is 14 days for those not allocated to early oral switch, and 5 days for those allocated to early oral switch.
2. (Flu)cloxacillin - Either intravenous flucloxacillin/cloxacillin 2 g every 4 or 6 h. The minimum protocol duration of allocated study treatment is 14 days for those not allocated to early oral switch, and 5 days for those allocated to early oral switch.
For MSSA, they will be randomised to:
1. Cefazolin - Intravenous cefazolin 2 g every 6 or 8 h. The minimum protocol duration of allocated study treatment is 14 days for those not allocated to early oral switch, and 5 days for those allocated to early oral switch.
2. (Flu)cloxacillin - as above
For MRSA, they will be randomised to
1. Combination of usual care (vancomycin or daptomycin) plus cefazolin (7 days) - In addition to standard treatment an intravenous β-lactam will be added for the first 7 calendar days following randomisation (day 1 being the day of randomisation - hence patients will receive 6-7 days of β-lactam). This β-lactam will be intravenous cefazolin 2 g every 8 h.
2. Usual care alone

- Early Oral Switch Domain:
If the participant is deemed eligible, and clinically stable at Day 7 or 14, they will be randomised to receive either:
1. Oral antibiotic regimen - Switch from intravenous backbone antibiotic for MRSA or MSSA or PSSA to oral antibiotics at the treating clinicians discretion on trial Day 7 (+/- 2 days) or trial Day 14 (+/- 2 days).
2. Continued intravenous antibiotic therapy.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)

Benzylpenicillin, cefazolin, flucloxacillin, vancomycin, daptomycin, clindamycin, amoxicillin, flucloxacillin, cefalexin, linezolid, moxifloxacin, ciprofloxacin, levofloxacin, rifampicin, trimethoprim plus sulfamethoxazole (TMP+SMX), fusidic acid, clindamycin, co-amoxiclav

Primary outcome(s)
All-cause mortality at 90 days after platform entry determined through a search of hospital databases for a record of a participant's death, or follow-up contact with the participant's community healthcare provider, or follow-up contact with the patient or their nominated carer, or linkage with death registries.

Key secondary outcome(s))
1. All-cause mortality at 14, 28 and 42 days after platform entry;
2. Duration of survival censored at 90 days after platform entry;
3. Length of stay of acute index inpatient hospitalisation for those surviving until hospital discharge (excluding HITH/COPAT/OPAT/rehab) truncated at 90 days after platform entry. Acute index hospitalisation is defined as a continuous admission to an inpatient healthcare facility where the patient was recruited;
4. Length of stay of total index hospitalisation for those surviving until hospital discharge (including HITH/COPAT/OPAT/rehab) truncated at 90 days after platform entry. Total index hospitalisation is defined as a continuous admission to any healthcare facility, including rehabilitation hospitals, and hospital-in-the-home or outpatient parenteral antimicrobial therapy services;
5. Time to being discharged alive from the total index hospitalisation (including HITH/COPAT /OPAT/rehab) truncated at 90 days after platform entry (and all deaths within 90 days will be considered '90 days');
6. Microbiological treatment failure defined as positive sterile site culture for S. aureus [of the same silo as the index isolate] between 14 and 90 days after platform entry). A sterile site means any sites deep to the skin and skin structures, including deep visceral and musculoskeletal abscesses that have been obtained in a sterile manner;
7. Diagnosis of new foci between 14 and 90 days after platform entry. The presence of new foci will be determined by the site investigator and can incorporate clinical, radiological, microbiological and pathological findings;
8. C. difficile diarrhoea as determined by a clinical laboratory in the 90 days following platform entry for participants ≥2 years of age. This means a stool submitted to a clinical laboratory has tested positive for C. difficile toxin or toxin gene;
9. Serious adverse reactions (SARs) in the 90 days following platform entry;
10. Health economic costs up to 1 year as detailed in the health economics appendix;
11. Proportion of participants who have returned to their usual level of function at day 90 as determined by whether the modified functional bloodstream infection score (FBIS) remained the same or improved between baseline and 90 days after platform entry

Completion date
31/12/2029

Eligibility

Key inclusion criteria
1. Staphylococcus aureus complex grown from ≥1 blood culture
2. Admitted to participating hospital at anticipated time of eligibility assessment
3. Appropriate consent has been obtained for the patient's participation in the trial

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Time of anticipated platform entry is greater than 72 h post collection of the index blood culture
2. Polymicrobial bacteraemia, defined as more than one organism (at species level) in the index blood cultures, excluding those organisms judged to be contaminants by the treating clinicians
3. Patient currently being treated with a systemic antibacterial agent that cannot be ceased or substituted for interventions allocated within the platform (unless antibiotic is listed in Table 1, which specifies allowed antibiotics with limited absorption from the gastrointestinal tract or negligible antimicrobial activity against S. aureus)
4. Known previous participation in SNAP
5. Known positive blood culture for S. aureus (of the same silo: PSSA, MSSA or MRSA) between 72 h and 180 days prior to the time of eligibility assessment
6. Treating team deems enrolment in the study is not in the best interest of the patient
7. Treating clinician believes that death is imminent and inevitable
8. Patient is for end-of-life care and antibiotic treatment is considered not appropriate
9. Patient <18 years of age and paediatric recruitment not approved at recruiting site
10. Patient has died since the collection of the index blood culture

Date of first enrolment
18/02/2022

Date of final enrolment
30/06/2027

Locations

Countries of recruitment
United Kingdom

Australia

Canada

Israel

Netherlands

New Zealand

Singapore

South Africa

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Research teams may approach the SNAP leadership with a formal data sharing request detailing the specific requirement, proposed research, qualification of researchers and publication plan if they are interested in using SNAP data. The request will be reviewed by the International Trial Steering Committee. If approved and once any additional ethics has been obtained data would be shared. Any data transfer will be anonymised, and considerations will be taken if non-aggregated data is requested. All participants will be consented for future use of their data.

IPD sharing plan summary

Available on request