Benzylpenicillin versus flucloxacillin or cloxacillin for the treatment of penicillin-susceptible *Staphylococcus aureus* bacteraemia (SNAP): an international, multicentre, open-label, non-inferiority randomised controlled trial

The Staphylococcus aureus *Network Adaptive Platform (SNAP) Trial Group*

Summary

Background Previously considered rare, penicillin-susceptible *Staphylococcus aureus* (PSSA) bacteraemia has re-emerged worldwide. Although benzylpenicillin might offer advantages in terms of pharmacokinetic and adverse effect profiles, anti-staphylococcal penicillins are recommended for serious infections because of concern over undetected penicillin resistance. We aimed to compare benzylpenicillin with anti-staphylococcal penicillins (cloxacillin or flucloxacillin) for the treatment of PSSA bacteraemia in adults.

Methods This investigator-initiated, international, multicentre, open-label, non-inferiority, randomised controlled trial was conducted within the PSSA silo of the backbone domain of the ongoing *S aureus* Network Adaptive Platform (SNAP) trial. We enrolled patients of all ages who were admitted with *S aureus* bacteraemia at 67 hospitals across Australia, New Zealand, Canada, Israel, the Netherlands, the UK, Singapore, and South Africa. Herein, we report results for adult patients (aged ≥18 years). Participants were randomly allocated 1:1 to receive either benzylpenicillin, or flucloxacillin or cloxacillin. Trial staff, staff caring for participants, and participants were aware of the treatment allocated and received. Cloxacillin was used only where flucloxacillin was not available (ie, Canada, Israel, Singapore, and South Africa). Recommended standard dosing for benzylpenicillin was 1·8 g intravenously once every 4 h or 2·4 g once every 6 h; for flucloxacillin 2·0 g intravenously once every 6 h; and for cloxacillin 2·0 g intravenously once every 4 h. The primary outcome was all-cause mortality 90 days after platform entry, assessed in the intention-to-treat population, including all patients with available data. The primary outcome was analysed by use of a hierarchical Bayesian logistic regression model, with non-inferiority of benzylpenicillin defined as an adjusted odds ratio (OR) of less than 1·20. Analyses occurred after every 500 participants reached 90-day follow-up. The SNAP trial is registered with ClinicalTrials.gov (NCT05137119) and is ongoing.

Findings Following the fourth interim analysis, the data and safety monitoring committee recommended ceasing recruitment before prespecified stopping thresholds were reached because of increased acute kidney injury (AKI) in participants receiving flucloxacillin or cloxacillin, and the PSSA silo was closed for recruitment on Aug 7, 2024. Between Feb 18, 2022, and June 21, 2024, of 493 adults with PSSA bacteraemia, 125 were randomly assigned to the flucloxacillin or cloxacillin group and 156 to the benzylpenicillin group. The median age was 67 years (IQR 56–77), 87 (31%) were female, and 194 (69%) were male. 21 (14%) of 152 in the benzylpenicillin group and 26 (22%) of 121 in the flucloxacillin or cloxacillin group met the primary outcome of death at 90 days (adjusted OR 0·67, 95% credible interval [CrI] 0·35–1·28), with a posterior probability of benzylpenicillin non-inferiority of 96·1% and of benzylpenicillin superiority of 88·9%. AKI occurred in 17 (11%) of 153 patients in the benzylpenicillin group and 27 (22%) of 124 patients in the flucloxacillin or cloxacillin group (adjusted OR 0·50, 95% CrI 0·26–0·94), corresponding to a posterior probability of non-inferiority of benzylpenicillin of 99·8% and superiority of benzylpenicillin of 98·4%. Seven total serious adverse reactions were reported from six (4%) of 156 participants in the benzylpenicillin group and ten were reported from nine (7%) of 125 participants in the flucloxacillin or cloxacillin group.

Interpretation Although the prespecified non-inferiority criterion for benzylpenicillin was not met, the probability of benzylpenicillin being non-inferior for mortality, along with a reduction in risk of AKI, indicates that benzylpenicillin should be preferred over flucloxacillin or cloxacillin for treatment of PSSA bacteraemia in adults.

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Research in context

Evidence before this study

We searched PubMed using the terms "penicillin-susceptible *Staphylococcus aureus*," "PSSA", "bacteraemia", "penicillin G", "benzylpenicillin", and "antistaphylococcal penicillins" for studies published from database inception to May 1, 2024. The current standard treatment for penicillin-susceptible *Staphylococcus aureus* (PSSA) bacteraemia is an anti-staphylococcal penicillin, such as flucloxacillin. Several observational studies have reported similar or superior outcomes with benzylpenicillin compared with anti-staphylococcal penicillins in PSSA bacteraemia. However, these were subject to limitations, including confounding by indication and immortal time bias. International guidelines have continued to recommend anti-staphylococcal penicillins over penicillin for serious infections, due to historical concerns about undetected penicillin resistance. No previous randomised controlled trial has directly compared benzylpenicillin with anti-staphylococcal penicillins in PSSA bacteraemia.

Added value of this study

To the best of our knowledge, this is the first randomised controlled trial comparing benzylpenicillin with flucloxacillin or cloxacillin for PSSA bacteraemia. Conducted within the international *Staphylococcus aureus* Network Adaptive Platform, the trial enrolled 281 adults who were admitted to participating hospitals. Benzylpenicillin showed a posterior probability of non-inferiority of 96·1% and superiority of 88·9% for the primary outcome of 90-day all-cause mortality. Benzylpenicillin was also associated with lower rates of acute kidney injury. The results were consistent in intention-to-treat and protocol-adherent analyses. The trial also showed the feasibility and reliability of modern phenotypic penicillin-susceptibility testing of *S aureus* across multiple international sites.

Implications of all the available evidence

These findings suggest that benzylpenicillin is at least as effective as and is safer than flucloxacillin or cloxacillin for PSSA bacteraemia and therefore should be preferred over anti-staphylococcal penicillins for treatment for adults with PSSA bacteraemia, where accurate laboratory testing for penicillin susceptibility is available.

Introduction

Staphylococcus aureus causes more than 1 million deaths per year globally.[1] *S aureus* bacteraemia, an invasive form of infection that can manifest as endocarditis, osteomyelitis, septic arthritis or in other foci, is associated with 3-month mortality rates exceeding 25% in adults.[2] Although there are established best clinical practices for *S aureus* bacteraemia,[3] the optimal antibiotic for the treatment of most forms of *S aureus* bacteraemia is unknown, resulting in substantial practice variation.[4]

Although once considered rare, penicillin-susceptible *S aureus* (PSSA) has been re-emerging internationally, and is responsible for up to 25% of all clinical *S aureus* isolates in some areas.[5–9] The anti-staphylococcal penicillins (eg, oxacillin, nafcillin, flucloxacillin, and cloxacillin) are resistant to degradation by penicillinase, the enzyme that hydrolyses penicillin. For *S aureus* endocarditis, anti-staphylococcal penicillins are preferred over penicillin in international guidelines due to the theoretical concern for misclassifying low-level producers of penicillinase as penicillin-susceptible.[10,11] However, the clinical implications of potential in-vitro misclassification are unknown, and modern testing strategies minimise this risk.[8,12] As anti-staphylococcal penicillins are considered the standard of care for PSSA infections in European and US guidelines,[10,11] we designed a trial to test the non-inferiority of benzylpenicillin to the anti-staphylococcal penicillins for mortality and compare the risk of harms.

Benzylpenicillin has several potential advantages compared with the anti-staphylococcal penicillins for the treatment of PSSA. First, benzylpenicillin has lower minimum inhibitory concentrations (MIC) by 10–50-fold,[13,14] which, when combined with higher free drug concentrations (average flucloxacillin protein binding is 93% and benzylpenicillin is 65%)[15] means substantially improved free drug time above the MIC. Second, benzylpenicillin has a highly bioavailable oral switch option in amoxicillin.[7,16] Third, benzylpenicillin has been associated with a lower risk of harms, such as phlebitis, hepatotoxicity, and renal toxicity, compared with flucloxacillin in observational studies.[17] Finally, several observational studies have suggested similar or superior outcomes when comparing penicillin with anti-staphylococcal penicillins for the management of PSSA bacteraemia.[18–21] Nonetheless, observational studies are subject to issues of immortal time bias and confounding by severity or indication. A randomised controlled trial is the best means of assessing the utility of penicillin for *S aureus* bacteraemia, including endocarditis. Within the *S aureus* Network Adaptive Platform (SNAP),[22] we undertook a pragmatic, non-inferiority, randomised controlled trial comparing benzylpenicillin with an anti-staphylococcal penicillin (cloxacillin or flucloxacillin) for the treatment of PSSA bacteraemia.

Methods

Study design and setting

SNAP is an investigator-initiated, international, multicentre, open-label, randomised controlled trial structured to address multiple clinical questions.[22] The platform uses a shared master protocol and statistical framework[23] with domain-specific appendices addressing

nested questions.[24,25] A domain refers to a management question, in which two or more interventions (eg, backbone antibiotics, adjunctive clindamycin therapy,[25] or early oral switch[24]) are compared (appendix 1 pp 23–24). The backbone antibiotic domain is further divided into silos based on *S aureus* antibiotic susceptibility: penicillin-susceptible; meticillin-susceptible, penicillin-resistant (MSSA); and meticillin-resistant. Participants could be enrolled in one or more domains.

Here, we report a non-inferiority comparison in the PSSA silo of the backbone antibiotic domain of SNAP. Participants were recruited between Feb 17, 2022, and June 21, 2024, at 67 hospitals in Australia, New Zealand, Canada, Israel, the Netherlands, the UK, Singapore, and South Africa, with the last patient reaching the 90-day outcome timepoint on Sept 19, 2024. The trial was conducted in accordance with the principles of the Good Clinical Practice and guidelines of the International Council for Harmonisation. Ethics and regulatory approval was obtained at each participating centre. Lead ethics approval was obtained from the Melbourne Health Research Ethics Office (EC00243; approval number 2021.048). Written or oral informed consent, in accordance with regional regulations, was obtained from all patients or their surrogates. The master protocol[22] and statistical analysis plan[23] have been described previously and, along with the domain-specific and statistical appendices for this trial, are available in appendix 2. The SNAP trial is registered with ClinicalTrials.gov (NCT05137119) and is ongoing. Patient and public representatives were involved in trial design, conduct and reporting of results, via a consumer reference group, which meets regularly and a consumer representative on the global trial steering committee.

International coordination was provided by the global coordinating centre at the University of Melbourne, (Melbourne, VIC, Australia). Within each participating region or country, study coordination and monitoring were provided by a sponsor who was responsible for the trial under each nation's laws and governance. The platform is overseen by an independent data and safety monitoring committee (DSMC) comprising clinical trialists with experience in critical care, infectious diseases, pharmacy, vaccines, and paediatrics, and an independent statistician with Bayesian adaptive platform expertise.

We enrolled patients of all ages who were admitted to participating hospitals with *S aureus* bacteraemia to SNAP. This paper describes adults (aged ≥18 years) enrolled in the PSSA silo. Data from the ongoing paediatric study will be subsequently reported. Participants were eligible if they had at least one blood culture positive for PSSA. Participants were excluded if they met one or more of the following exclusion criteria: time of anticipated enrolment was more than 72 h after collection of the first positive blood culture (index blood culture); polymicrobial bacteraemia (excluding those judged to be contaminants); known previous participation in SNAP; known positive blood culture for *S aureus* between 72 h and 180 days before the time of assessment; treating team deemed enrolment not in best interests of the patient; death was imminent and inevitable; and the patient's goals of care did not include antibiotic therapy. Additional domain-specific exclusion criteria were: history of type I hypersensitivity reaction or severe delayed reaction to any penicillin or cephalosporin; history of a non-severe rash to any penicillin; current receipt of maintenance dialysis (haemodialysis or peritoneal dialysis); and treatment with additional systemic antibacterial agents with *S aureus* activity that cannot be ceased or substituted. Sex at birth was collected as self-reported or as reported in the medical records. Gender data were not collected. Ethnicity was collected as self-reported or as reported in the medical records, depending on the site. Platform entry refers to the time a patient was deemed eligible and consented for the core platform. Domain entry refers to the time a patient was deemed eligible for the relevant domain.

See Online for appendix 1

Randomisation and masking

Study staff enrolled participants and were involved in ongoing follow-up of participants. Participants were randomly assigned in a 1:1 ratio to receive either benzylpenicillin, or flucloxacillin or cloxacillin (cloxacillin where flucloxacillin was not available [ie, Canada, Israel, Singapore, and South Africa]). Randomisation was conducted by simple randomisation without stratification at enrolment into the platform. Eligibility assessment and randomisation was conducted with an electronic data capture system (Spiral Software). Randomised allocation was only revealed once eligibility for the PSSA silo of the backbone antibiotic domain was confirmed. Trial staff, staff caring for the participants, and participants were aware of the treatment allocated and received.

See Online for appendix 2

For more on **Spiral Software** see https://spiral.co.nz/

Procedures

Recommended standard dosing for benzylpenicillin was 1·8 g (3 million units) intravenously once every 4 h or 2·4 g (4 million units) once every 6 h, with dosing at the discretion of the treating clinician; for flucloxacillin 2·0 g intravenously once every 6 h; and for cloxacillin 2·0 g intravenously once every 4 h. Recommended adjusted dosing for renal dysfunction, critical illness, and continuous infusion are provided in appendix 1 (pp 28–29). Renally adjusted dosing was not recommended for cloxacillin, as per Canadian University Health Network dosing guidelines.[26] Co-administration of additional antibiotics for the treatment of *S aureus* bacteraemia was discouraged, apart from clindamycin in those also enrolled in the adjunctive treatment domain.[25]

The protocol recommended that allocated antibiotics be continued for the entire intravenous treatment duration, with a minimum antibiotic duration of 14 days

for uncomplicated bacteraemia and a range of 28–42 days for complicated bacteraemia. Subsequent randomisation to the early oral switch domain[24] was permitted at either 7 days or 14 days from platform entry for eligible participants. Apart from the anti-staphylococcal antibiotics used, clinical management was left to the treating clinician's discretion; however, formal infectious diseases consultation[27] was advised and available at all sites. Participants were followed-up to day 90 after platform entry, with data collected at platform days 7, 14, 28, 42, and 90. Data were collected about the clinical course, laboartory results, hospitalisation, treatment received, and vital status.

The determination of penicillin susceptibility is described in more detail in appendix 1 (pp 33–34). Briefly, at each site's clinical laboratory, automated testing was initially performed as a screening test and then susceptible isolates were confirmed by use of disc diffusion with reading of the zone diameter and zone-edge, or PCR for *blaZ* (the gene coding for the penicillinase that causes penicillin resistance in *S aureus*). Both the Clinical and Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) disc diffusion methods were permitted based on regional practices; however, if available, the EUCAST method was recommended based on our validation.[12]

Outcomes

The primary outcome was all-cause mortality 90 days after platform entry. Secondary outcomes included: all-cause mortality at 14, 28, and 42 days; microbiological treatment failure (defined as positive sterile site culture for *S aureus* 15–90 days after platform entry); diagnosis of new foci of infection between platform days 15 and 90; and *Clostridioides difficile* infection within 90 days (appendix 1 pp 30–31; appendix 2 pp 38–41). Secondary domain-specific outcomes (further defined in appendix 1 pp 31–32) included: acute kidney injury (AKI), defined as an absolute creatinine increase of 26·5 µmol/L (0·3 mg/dL) or more within 5 days of platform entry or a relative increase of 50% or more from baseline (ie, day of platform entry) within the first 14 days; initiation of renal replacement therapy up to day 90; ongoing renal replacement therapy at day 90; hepatotoxicity, defined as alanine aminotransferase (ALT) or γ-glutamyl transferase (GGT) increasing above 2·5 times the upper limit of normal (defined as 30 IU/L for males and 19 IU/L for females for ALT and 60 IU/L for males and 40 IU/L for females for GGT) within 14 days; change in assigned antibiotic therapy due to an adverse event; change in assigned therapy due to presumed lack of efficacy (due to inadequate clinical response) according to the treating team; and peripherally inserted central catheter or other central venous catheter complications requiring line removal while on assigned therapy. Data on serum creatinine and liver function tests were systematically collected for all participants at baseline, days 1–5, and days 6–14.

In addition, after the MSSA and PSSA silos of the antibiotic backbone domain were closed for recruitment, but before unblinding and analysis, we added a secondary outcome of treatment failure at 90 days, to allow a more direct comparison with the randomised controlled trials for daptomycin[28] and ceftobiprole,[29] which led to their approval for the treatment of *S aureus* bacteraemia. Treatment failure was defined to have occurred if the patient died (by day 90) or had microbiological treatment failure or a diagnosis of new infectious foci between platform day 15 and 90.

Assessments of outcomes for each individual participant were performed by trial site staff with knowledge of the allocated status of that participant. Analyses of aggregated outcomes were performed by the unblinded analytical team for scheduled analyses. All other trial investigators remained masked to analyses of the aggregated outcomes until the MSSA and PSSA silos of the antibiotic backbone domain were closed for recruitment and final analyses presented.

In addition to the prespecified safety outcomes that were systematically defined and assessed, site investigators were asked to report all serious adverse reactions that were thought to be possibly, probably, or definitely related to the study drug or study procedures, and to conform to any additional regional safety reporting requirements.

Statistical analysis

Populations were defined based on the intention-to-treat principle for each estimand corresponding to the randomised treatment assignment, regardless of receipt of the intervention. The primary outcome analysis was also performed on a protocol-adherent population (appendix 1 pp 35–36), which included all of the following patients: those who died, were discharged from hospital, or were randomly assigned to early oral switch before day 7 (ie, on day x) and received at least x–1 days of the allocated drug; and those who remained on allocated treatment for 7 or more days (x days) and received at least x–2 days of the allocated drug.[24] The protocol-adherent population must also have received no more than one dose of the alternative antibiotic (ie, the antibiotic of the group they were not assigned to) between allocation reveal and platform day 14.

The scheduled and final analyses were performed by an unblinded analytical team and reported to the DSMC. Communications between the analytical team and the trial investigators were strictly restricted according to terms of reference and trial integrity procedures. The analyses are described in full in the statistical analysis plan (appendix 2 pp 108–182) and as previously published.[30] Unblinded results were provided to the investigator team only after domain closure and finalisation of the statistical analysis plan.

The primary outcome was to establish whether benzylpenicillin is non-inferior to flucloxacillin or cloxacillin in terms of 90-day all-cause mortality, with non-inferiority defined as an adjusted odds ratio (OR) less than 1·20. The adjusted OR for the primary outcome was calculated by use of a hierarchical Bayesian logistic regression model,[23] and is reported along with 95% credible intervals (CrIs). This model incorporated data from all platform participants with adjustment for age, country, temporal epoch (contiguous 26-week periods from the start of the platform), and eligibility and treatment assignment in other platform domains.[23–25] Details of the model fitting and diagnostics are provided in appendix 1 (pp 36–37). The treatment effect pertaining to benzylpenicillin versus flucloxacillin or cloxacillin was calculated exclusively by use of patients in the PSSA silo's randomised comparison, with prespecified information sharing from the 14 paediatric participants enrolled in this silo. Here, we report only on the treatment effect for adults. The primary analysis for the primary outcome excluded participants with missing 90-day mortality data (complete case analysis). We also conducted post-hoc sensitivity analyses in which all participants whose day 90 mortality data were missing were assumed to have survived or to have died.

Binary secondary outcomes were analysed as per the primary outcome. However, for the prespecified secondary outcome of treatment failure, to compare with the US Food and Drug Administration's accepted criteria for *S aureus* bacteraemia trials, a non-inferiority margin of adjusted OR of less than 1·85 was also estimated (corresponding to 15% on the absolute scale for control event rates below 36·5%) and an adjusted risk difference was estimated from this OR and the average control event rate. For time-to-event outcomes, we planned a survival analysis using a Bayesian Weibull proportional hazards model; however, this model's assumptions were not satisfied and hence we present unadjusted Kaplan–Meier curves. Prespecified subgroup analyses included analyses of people with or without infective endocarditis, people who inject drugs, and pregnant participants, and subgroup analysis by ethnicity. Microbiologically defined subgroups (eg, by the PCR-detected presence of the penicillinase gene, *blaZ*) will be published in a future publication once all isolates have been fully characterised at a central reference laboratory. As analyses were conducted in a Bayesian framework, we report the means of the posterior distributions of treatment effects with 95% CrIs and, where appropriate, associated posterior probabilities. No p values were calculated, and no adjustment for multiple analyses was prespecified. Therefore, for the secondary estimands, excluding safety outcomes, the 95% CrIs should not be used to draw definitive conclusions, and apart from the safety outcome of AKI and the secondary outcome of treatment failure, the posterior probabilities for non-inferiority and superiority are not reported. Analyses were conducted using R version 4.3.1. Bayesian models were fit using Stan[31] via the rstan R package version 2.32.7.

As an adaptive Bayesian platform, simulations were conducted with a maximum sample size of 7000 to optimise trial operating characteristics, such as the number and timing of interim analyses and decision-rule thresholds. Scheduled analyses were conducted after every 500 patients enrolled in the platform reached day 90 with prespecified stopping rules applied at each analysis for each domain and silo. For the PSSA silo of the backbone antibiotic domain, decision criteria were as follows: if the posterior probability of non-inferiority (defined as adjusted OR <1·20) for benzylpenicillin was greater than 99% in adults, the independent DSMC could recommend stopping recruitment; if the posterior probability of the adjusted OR <0·83 was less than 1%, the DSMC could recommend stopping for futility of achieving the superiority objective. If no threshold was met, recruitment was to continue, unless the DSMC had substantial safety concerns, which were not prespecified.

The non-inferiority margin and posterior probability threshold of 99% were informed by simulations indicating an acceptable type I error and feasible recruitment rates. Under the assumption of a 90-day mortality rate of 15% in the control group, the non-inferiority margin of an adjusted OR of less than 1·20 would translate to an absolute difference in 90-day mortality of approximately 2·5%, which is substantially lower than non-inferiority margins used in *S aureus* bacteraemia drug registrational trials of 20%[28] and 15%[29] for an outcome of treatment failure. For reporting, superiority was defined as an adjusted OR of less than 1·00. For the secondary outcome of AKI, we used the same non-inferiority and superiority cutoffs for reporting.

At the first (July 5, 2023), second (Nov 6, 2023), and third (Feb 21, 2024) DSMC reviews of interim analyses, the DSMC recommended continuing with the trial according to the protocol with no changes. On June 21, 2024, at the fourth planned interim analysis, the DSMC requested recruitment be paused in the PSSA and MSSA silos of the backbone antibiotic domain because of a safety signal involving AKI seen in both silos. Subsequently, on Aug 5, 2024, the DSMC recommended closing both the MSSA and PSSA silos because the statistical stopping threshold for non-inferiority had been met in the MSSA silo, and the safety signal for AKI with flucloxacillin or cloxacillin was confirmed in both silos. On Aug 7, 2024, without additional knowledge of study outcomes, the trial steering committee accepted the recommendation and the MSSA and PSSA silos were closed for recruitment. Recruitment to SNAP is ongoing and to maintain trial integrity, the results for the paediatric patients, the MRSA silo, and other domains remain blinded.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Trial sites were open to enrol into the PSSA silo of the backbone antibiotic domain from Feb 18, 2022, until June 21, 2024. Of 8546 patients screened, 2821 were recruited to SNAP (appendix 1 p 38). The most common reason for platform exclusion was that more than 72 h had elapsed since the collection of the index blood culture. Of the 2821 patients who were recruited, 493 adults had PSSA bacteraemia and were screened for eligibility, 281 of whom were eligible and consented to participate. Of the 281 adults, 125 were randomly assigned to the flucloxacillin or cloxacillin group and 156 to the benzylpenicillin group (figure). Eight participants were withdrawn or lost to follow-up before 90 days, leaving 273 participants in the intention-to-treat population for the primary outcome.

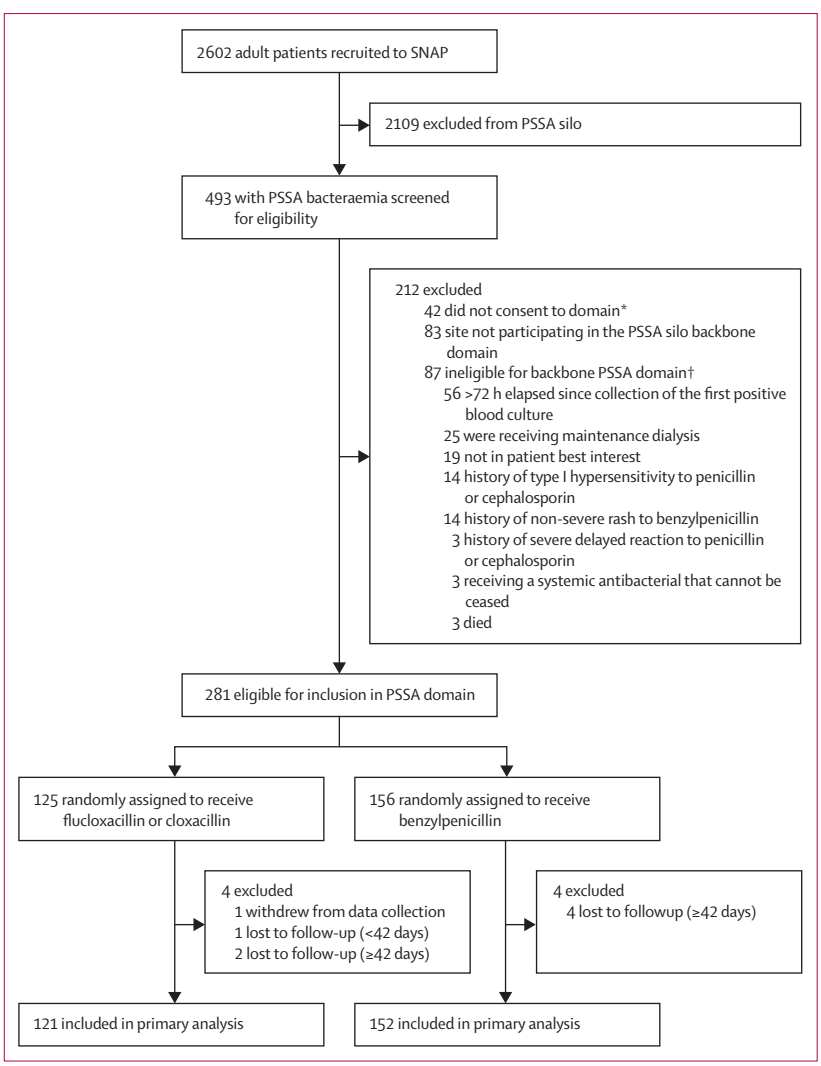

Figure: **Trial profile**
PSSA=penicillin-susceptible *Staphylococcus aureus*. SNAP=*Staphylococcus aureus* Network Adaptive Platform. *Includes consent not sought. †Participants could meet more than one exclusion criteria.

In the 281 participants enrolled, the median age was 67 years (IQR 56–77), 87 (31%) were female, and 194 (69%) were male, which is representative of a typical cohort with *S aureus* bacteraemia (appendix 1 pp 44–48). Baseline characteristics are presented in table 1. The most common source of infection was osteoarticular infection (85 [30%] of 281 patients; table 2). Antibiotics received between index blood culture collection and platform entry are presented in appendix 1 (pp 49–50). Of the 156 patients in the benzylpenicillin group, 84 (54%) had received flucloxacillin or cloxacillin between index blood culture collection and platform entry, compared with 66 (53%) of 125 patients in the flucloxacillin or cloxacillin group. Two of the 67 sites used *blaZ* PCR as the method to detect PSSA, accounting for four (1%) of 281 participants.

The estimated median duration of antibiotic treatment was 39 days (IQR 21–58) for the benzylpenicillin group and 42 days (18–52) for the flucloxacillin or cloxacillin group (appendix 1 pp 56–57). Specialist infectious diseases consultation was received for 153 (98%) of 156 participants in the benzylpenicillin group and 122 (98%) of 125 participants in the flucloxacillin or cloxacillin group.

21 (14%) of 152 patients with 90-day mortality data in the benzylpenicillin group and 26 (21%) of 121 patients with 90-day mortality data in the flucloxacillin or cloxacillin group met the primary outcome of death at 90 days (adjusted OR 0·67, 95% CrI 0·35–1·28) corresponding to a posterior probability of benzylpenicillin non-inferiority of 96·1% and of benzylpenicillin superiority of 88·9% (table 3).

Secondary outcomes are presented in table 3. The key secondary outcome of AKI was observed in 17 (11%) of 153 participants in the benzylpenicillin group and 27 (22%) of 124 in the flucloxacillin or cloxacillin group (adjusted OR 0·50, 95% CrI 0·26–0·94), corresponding to a posterior probability of non-inferiority of benzylpenicillin of 99·8% and superiority of benzylpenicillin of 98·4%. The staging of AKI is presented in appendix 1 (p 51); 28 (64%) of 44 AKI episodes were grade 1 (mild). Renal replacement therapy was required in three (2%) of 156 participants in the benzylpenicillin group and five (4%) of 125 in the flucloxacillin or cloxacillin group; no participants required ongoing renal replacement therapy if alive at day 90.

Treatment failure occurred in 32 (22%) of 148 participants in the benzylpenicillin group versus 32 (28%) of 113 in the flucloxacillin or cloxacillin group (adjusted OR 0·75, 95% CrI 0·42 to 1·33; posterior probability of non-inferiority of benzylpenicillin was 99.9%; adjusted risk difference –5·5%, 95% CrI –14·1% to 6·1%). Other secondary outcomes are

presented in table 3 and appendix 1 (pp 40, 42–43, 56–57). More participants had their treatment changed due to clinician-determined presumed lack of efficacy in the benzylpenicillin group (11 [7%] of 156 participants) than in the flucloxacillin or cloxacillin group (one [1%] of 125 participants).

122 (78%) of 156 participants in the benzylpenicillin group and 103 (82%) of 125 participants in the flucloxacillin or cloxacillin group met the protocol-adherent population definition. The protocol-adherent population analysis for the primary outcome of 90-day mortality showed a posterior probability of non-inferiority of benzylpenicillin of 99·6% and superiority of 98·4% (table 3). There were only 23 patients with available data in the subgroup with endocarditis, hence no meaningful conclusions can be drawn, but the direction of effect was similar to the no endocarditis subgroup (lower crude mortality in the benzylpenicillin group; table 3). Other prespecified subgroups were too small for further analysis: pregnancy (n=0), and ethnicity in New Zealand (n=12 for Pacific Islander or Māori). In a post-hoc analyses accounting for the eight (3%) of 281 patients who had missing data for the primary outcome, the direction and approximate magnitude of effect on mortality was similar to that in the primary (complete case) analysis (table 3). Examining flucloxacillin and cloxacillin separately made no difference to the findings, neither for the primary outcome (90-day mortality was 14% [21/152] for benzylpenicillin, 21% [18/86] for flucloxacillin, and 23% [8/35] for cloxacillin) nor for the key secondary outcome of AKI (11% [17/153] for benzylpenicillin, 23% [20/87] for flucloxacillin, and 19% [7/37] for cloxacillin; appendix 1 p 58). Seven total serious adverse reactions were reported from six (4%) of 156 participants in the benzylpenicillin group and ten were reported from nine (7%) of 125 participants in the flucloxacillin or cloxacillin group (appendix 1 pp 52–53).

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)
Demographics		
Age, years	65·5 (55·8–75·2)	69·0 (57·0–79·0)
Sex		
Female	46 (29%)	41 (33%)
Male	110 (71%)	84 (67%)
Weight, kg	80·0 (70·0–97·0)	82·0 (70·0–95·0)
Comorbidities		
Diabetes	48 (31%)	43 (34%)
Chronic kidney disease*	20 (13%)	14 (11%)
Cirrhosis	7 (4%)	8 (6%)
Cancer requiring any surgical or medical therapy within 12 months †	16 (10%)	15 (12%)
Dementia	10 (6%)	6 (5%)
Iatrogenic immunosuppression‡	19 (12%)	16 (13%)
Implanted intravascular prosthesis or endovascular device§	15 (10%)	16 (13%)
Previous infective endocarditis	4 (3%)	2 (2%)
Underlying cardiac abnormality predisposing to endocarditis¶	13 (8%)	5 (4%)
Injection drug use within 6 months	7 (4%)	5 (4%)
Limitations to care‖	21 (13%)	19 (15%)
Prognostic factors		
Time from index blood culture collection to index blood culture positivity, hours	16·4 (12·4–21·2)	14·9 (12·0–18·1)
Time from index blood culture to platform entry, hours	54·4 (44·4–65·1)	49·0 (39·9–64·9)
Time from index blood culture to domain entry, hours	63·4 (54·3–68·2)	63·7 (51·5–68·1)
Admitted to intensive care unit at time of recruitment	23 (15%)	11 (9%)
Median Pitt Bacteraemia Score	0 (0–1)	0 (0–1)
Median C-reactive protein, mg/L	184 (125·8–268·5)	194·0 (126·0–276·0)
Receipt of antibiotics between index blood culture and platform entry	155 (99%)	124 (99%)
Clinical quality indicators		
Review by infectious disease specialist**	153 (98%)	122 (98%)

Data are n (%) or median (IQR). *Defined as estimated glomerular filtration rate below 50 mL/min per 1·72 m². †Excluding non-melanoma skin cancers. ‡Defined as patients who, within past 3 months, have received any of the following: prednisone 0·5 mg/kg per day or more (or equivalent) for more than 14 days; ciclosporin, tacrolimus, or sirolimus; azathioprine, leflunomide, or mycophenolate; cyclophosphamide or methotrexate; monoclonal antibodies such as infliximab; cancer chemotherapy; bone marrow transplantation; other immunosuppressive agents equal to those mentioned. §Not including central lines, whether temporary or tunnelled. ¶Excluding implanted intravascular prosthesis or endovascular device. ‖Defined as active orders or advance care directives limiting resuscitation and intensive care admission. **During index hospitalisation, which excludes time when transferred to another acute care facility where further data may not be available.

Table 1: **Baseline characteristics of adult patients**

Discussion

In this trial, which was concluded before a statistical trigger was met for non-inferiority, the posterior probability of non-inferiority of benzylpenicillin compared with flucloxacillin or cloxacillin in adults with PSSA bacteraemia for 90-day mortality was 96·1%, and of superiority was 88·9%. Benzylpenicillin was less nephrotoxic than flucloxacillin or cloxacillin, with approximately half the rate of AKI. These findings suggest that benzylpenicillin should be preferred to anti-staphylococcal penicillins, such as flucloxacillin or cloxacillin, for treatment of PSSA bacteraemia in adults.

Due to concerns of falsely reporting penicillin susceptibility, international guidelines recommend that patients with endocarditis due to any MSSA strain, regardless of penicillin susceptibility, should be treated with anti-staphylococcal penicillins, such as flucloxacillin or cloxacillin, as first-line therapy.[10,11] Moreover, whether clinical laboratories should test for and report penicillin susceptibility has been controversial.[12] Some laboratory assays have poor sensitivity for detection of penicillinase leading to fears of inappropriately reporting penicillin susceptibility. Both the CLSI and EUCAST guidelines recommend against relying on automated antimicrobial susceptibility testing alone for penicillin susceptibility and state that laboratories should perform confirmatory

phenotypic testing with a penicillin disc test.[32,33] The combination of automated antimicrobial susceptibility testing and phenotypic disc testing with reading of the zone edge (as used in this trial) is highly sensitive, with reported false negative rates of 0·7% (EUCAST) to 1·4% (CLSI).[10–12] Given that only participants with PSSA confirmed by phenotypic disc diffusion or the absence of *blaZ* gene on PCR were eligible for inclusion, the trial findings should not be extended to patients in whom only automated antimicrobial susceptibility testing has been performed without additional confirmatory testing.

The SNAP trial protocol mandated that either CLSI or EUCAST disc phenotype testing, or *blaZ* PCR be performed in clinical laboratories at each trial site to confirm penicillin susceptibility, with results available and participants enrolled within 72 h of blood culture collection. Within this pragmatic setting, these trial results indicate that penicillin-susceptibility testing can safely guide treatment decisions. Furthermore, the results suggest that testing for penicillin susceptibility and then treating infections due to susceptible isolates with benzylpenicillin is likely to be more clinically effective and less toxic than an approach that treats all MSSA infections with an anti-staphylococcal penicillin.

We also assessed a composite treatment failure outcome with a non-inferiority margin similar to the absolute margin of 15% as used in antibiotic registrational trials for *S aureus* bacteraemia.[28,29] The observed treatment failure rates of 22% with benzylpenicillin and 28% with flucloxacillin or cloxacillin (adjusted risk difference of –5·5% [95% CrI –14·1% to 6·1%]) would meet the non-inferiority margins that led to the approval of daptomycin and ceftobiprole for *S aureus* bacteraemia.

Although anti-staphylococcal penicillins should no longer be considered the standard of care for adults with PSSA bacteraemia, whether benzylpenicillin or cefazolin should be preferred is a question that remains unanswered. On the one hand, benzylpenicillin provides a relatively narrow spectrum of activity, with both an excellent predicted time above the MIC and easy oral transition option to amoxicillin, which is highly bioavailable.[7,16] On the other hand, cefazolin has a longer half-life, allowing for less frequent dosing and a lower chance of allergy than benzylpenicillin.[34,35]

Our findings should be interpreted in the context of other clinical trials for *S aureus* bacteraemia, which are either recently completed or currently recruiting. In another SNAP trial domain, cefazolin has been compared with flucloxacillin or cloxacillin for MSSA.[36] The CloCeBa trial has compared cefazolin with cloxacillin for MSSA, and found that cefazolin was non-inferior to cloxacillin and caused less AKI, consistent with our results in PSSA.[35] The COMeBAC trial (NCT06726395), comparing benzylpenicillin with cloxacillin for PSSA, is ongoing.

In contrast to most infectious diseases trials, this trial was global, with sites from North America, Europe, Asia, Australia, and New Zealand. However, nearly all participating sites in this trial were in high-income countries, potentially limiting generalisability to low-income and middle-income settings.

We have not reported the proportion of participants who were allocated to interventions that are part of ongoing SNAP domains (specifically adjunctive clindamycin versus no clindamycin, and early oral switch versus entirely intravenous therapy); this is necessary to preserve blinding and trial integrity, but could affect how clinicians interpret the results. The other domains use 1:1 randomisation and thus these treatments are likely equally distributed in the benzylpenicillin and flucloxacillin or cloxacillin groups. Furthermore, inclusion and treatment assignment in other domains was adjusted for in the statistical model for the analysis reported here.

This trial has some limitations. First, this was an open-label trial; hence, clinical decisions were taken with knowledge of treatment assignment. For instance, it is likely that the higher proportion of change of antibiotic due to perceived inadequate treatment response in the benzylpenicillin group reflects underlying fears that

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)
Osteoarticular (including epidural abscess)	49 (31%)	36 (29%)
Septic arthritis and extra-axial osteomyelitis	27 (17%)	19 (15%)
Vertebral osteomyelitis or septic discitis	10 (6%)	4 (3%)
Epidural abscess	14 (9%)	8 (6%)
Orthopaedic hardware-associated bone and joint infection	4 (3%)	6 (5%)
Skin and soft tissue	45 (29%)	30 (24%)
Isolated skin and soft tissue	32 (21%)	20 (16%)
Primary bacteraemia†	20 (13%)	19 (15%)
Intravascular catheter associated	17 (11%)	20 (16%)
Isolated intravascular catheter infection	16 (10%)	17 (14%)
Endocarditis	8 (5%)	15 (12%)
Left-sided native valve	7 (4%)	10 (8%)
Right-sided native valve	2 (1%)	6 (5%)
Prosthetic valve	0	1 (1%)
Cardiac or other implantable non-orthopaedic device	14 (9%)	8 (6%)
Other deep focus	7 (4%)	3 (2%)
Pleuropulmonary	4 (3%)	4 (3%)
Genitourinary	4 (3%)	4 (3%)
Central nervous system	2 (1%)	1 (1%)

Data are n (%). *More than one focus could be included for each patient. †Primary bacteraemia refers to cases where no other focus of infection is clinically apparent.

Table 2: **Focus of infection***

	Benzylpenicillin (n=156)	Flucloxacillin or cloxacillin (n=125)	Median-adjusted odds ratio (95% CrI)	Posterior probability of benzylpenicillin non-inferiority*†	Posterior probability of benzylpenicillin superiority†‡
Primary outcome: 90-day all-cause mortality					
Primary analysis population	21/152 (14%)	26/121 (21%)	0·67 (0·35–1·28)	96·1%	88·9%
Protocol-adherent population	9/122 (7%)	19/103 (18%)	0·43 (0·19–0·93)	99·6%	98·4%
Secondary outcomes					
Acute kidney injury§¶	17/153 (11%)	27/124 (22%)	0·50 (0·26–0·94)	99·8%	98·4%
14-day mortality	10/156 (6%)	8/125 (6%)	1·14 (0·47–2·76)	NE	NE
28-day mortality	13/156 (8%)	16/124 (13%)	0·77 (0·36–1·62)	NE	NE
42-day mortality	18/156 (12%)	17/123 (14%)	1·00 (0·49–2·00)	NE	NE
Change of antibiotic due to perceived inefficacy	11/156 (7%)	1/125 (1%)	5·82 (1·74–30·28)	NE	NE
Microbiological treatment failure after day 14	6/141 (4%)	3/106 (3%)	1·30 (0·42–4·00)	NE	NE
Diagnosis of new foci of infection after day 14	7/143 (5%)	6/113 (5%)	0·90 (0·33–2·40)	NE	NE
Treatment failure by day 90§‖	32/148 (22%)	32/113 (28%)	0·75 (0·42–1·33)	99·9%	NE
Change of antibiotic due to any adverse event§	8/156 (5%)	10/125 (8%)	0·79 (0·31–1·99)	NE	NE
Any serious adverse reaction related to study drug§	6/156 (4%)	9/125 (7%)	0·79 (0·29–2·02)	NE	NE
New renal replacement therapy within 90 days§	3/156 (2%)	5/125 (4%)	0·57 (0·17–1·79)	NE	NE
Ongoing renal replacement therapy at 90 days§	0/155 (0%)	0/123 (0%)	0·59 (0·07–3·81)	NE	NE
Hepatotoxicity within 14 days§**	18/145 (12%)	17/107 (16%)	0·76 (0·37–1·50)	NE	NE
Clostridioides difficile infection§	0/156 (0%)	1/123 (1%)	0·39 (0·05–2·07)	NE	NE
Intravenous catheter complication requiring removal§	7/156 (4%)	6/125 (5%)	0·84 (0·31–2·18)	NE	NE
Prespecified subgroup analysis: 90-day mortality					
No endocarditis subgroup	20/143 (14%)	23/106 (22%)	0·69 (0·34–1·33)	NE	NE
Endocarditis subgroup	1/8 (13%)	3/15 (20%)	0·99 (0·17–5·40)	NE	NE
Post-hoc analysis assuming all those with missing primary outcome data are either alive or dead					
All missing assumed to be dead at 90 days	25/156 (16%)	30/125 (24%)	0·68 (0·3, 1·22)	NE	NE
All missing assumed to be alive at 90 days	21/156 (13%)	26/125 (21%)	0·70 (0·37–1·32)	NE	NE

Data are n/N (%) unless otherwise specified. AKI=acute kidney injury. CrI=credible interval. NE=not estimated. *Non-inferiority was defined as an adjusted odds ratio of less than 1·20 for the primary endpoint of 90-day all-cause mortality, the key safety outcome of AKI, and the composite outcome of treatment failure. †Posterior probabilities are not reported for secondary outcomes, with the exception of the key safety outcome of AKI and the composite outcome of treatment failure. ‡Superiority was defined as an adjusted odds ratio of less than 1·00 for the primary endpoint of 90-day all-cause mortality and the key safety outcome of AKI. §These prespecified safety secondary outcomes were collected for all participants; numerators and denominators are provided to indicate where data was missing or unavailable. ¶Defined as an absolute creatinine increase of 26·5 µmol/L (0·3 mg/dL) or more within 5 days of platform entry or a relative increase of 50% or more from baseline within the first 14 days. ‖Non-inferiority for this comparison only was defined as an adjusted odds ratio of less than 1·85 for the composite outcome of treatment failure. **Defined as alanine aminotransferase or γ-glutamyl transferase increasing above 2·5 times the upper limit of normal within 14 days.

Table 3: **Primary and secondary outcomes**

penicillin-susceptibility testing might not be accurate. However, the overall risk of bias is mitigated by the objective primary outcome of all-cause mortality at 90 days, and the key safety outcome of AKI as determined by serial measurements of serum creatinine. Second, cloxacillin and flucloxacillin were the anti-staphylococcal penicillins used, whereas countries such as the USA generally use nafcillin or oxacillin. However, the chemical structures and anti-staphylococcal activity[37] of the entire class are similar. In a recent systematic review and meta-analysis comparing different anti-staphylococcal penicillins to each other and to cefazolin, no important differences in treatment outcomes or important toxic effects were shown between the members of the anti-staphylococcal penicillins.[34] Third, the dose of cloxacillin investigated was 12 g per day as recommended in Canadian antibiotic treatment guidelines, without adjustment for renal function. The results, particularly regarding AKI, might not be generalisable to lower doses of cloxacillin. Fourth, as a pragmatic trial, we had little control over downstream physician decisions. When patients have persistent bacteraemia, physicians often

feel compelled to act by changing the antibiotics. However, this type of downstream change reflects real clinical practice; patients were analysed by use of the intention-to-treat principle, and the protocol-adherent population showed results consistent with the intention-to-treat population. Fifth, the data reported here might not apply to children, particularly with regards to the risk of AKI. Sixth, most AKI episodes were grade 1 (mild). This result could be interpreted to mean that the observed AKI episodes were unimportant. However, the requirement for new renal replacement therapy, and AKI episodes that were reported by sites as serious adverse reactions were both numerically more common in the flucloxacillin or cloxacillin group, suggesting that the excess of AKI in the flucloxacillin or cloxacillin group represents clinically meaningful harm. Finally, the trial was concluded before prespecified triggers within this silo and domain were met, which resulted in a smaller sample size than intended. As we used simple randomisation, the smaller sample size also resulted in an imbalance in the number of allocations to each treatment group by chance. Early stopping of trials might also contribute to exaggerated estimates of treatment effects.[38] However, this is less likely to apply to the treatment failure outcome because an adequate sample size required for detecting a 15% non-inferiority margin would have been realised for all possible control event rates. Taken together, the likelihood of improved effectiveness and a better safety profile indicate that benzylpenicillin should be preferred to flucloxacillin or cloxacillin for treatment of PSSA bacteraemia.

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Contributors
SYCT and TCL are joint senior authors and contributed equally to the Article. JSD, SYCT, and TCL wrote the paper with early input from all authors. JSD wrote the first draft of the manuscript. RKM, GN, AM, and MD analysed the data. SYCT, JSD, GN, RKM, AM, and MD take responsibility for the integrity of the data and accuracy of the data analysis. GN, RKM, AM, and MD had full access to all the data for the paper. For each trial site, each site investigator directly accessed and verified the underlying data. Site monitoring of data to verify the underlying data occurred in each region under the supervision of regional trial management teams. The Penicillin and Methicillin-Susceptible Silos Domain Specific Working Group, the Global Trial Steering Committee, and the Statistics Working Group were responsible for the concept and design (appendix 1 p 13). Site investigators were responsible for data collection (appendix 1 pp 17–21). All authors were responsible for critical revision of the manuscript for important intellectual content. RKM, AM, and MD carried out the statistical analysis. The Global Trial Management Group and Regional Trial Management Groups were responsible for administrative, technical, or material support (appendix 1 p 15).

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Data sharing

De-identified patient data will be made available 12 months after publication of each primary results manuscript. Note that data related to trial domains which have not yet been publicly reported in peer reviewed publications will not be available. Thus, some of the analyses might not be completely reproducible except by the analytical team, which has access to all the unblinded data. Requesters will be required to complete a data access request form, which will be reviewed for approval by the Global Trial Steering Committee. All requests for data must be accompanied by a study proposal with clear statement of aims and hypotheses, and a statistical analysis plan. Applications from investigators with suitable academic capability to conduct the proposed work will be given consideration. If a proposal is approved, a signed data transfer agreement will be required before data sharing. The SNAP trial data access request form is available on the SNAP trial website: https://www.snaptrial.com.au/for-investigators#resource.

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