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Multicentre randomised double-blind placebo controlled trial of combination vancomycin and cefazolin surgical antibiotic prophylaxis: the Australian surgical antibiotic prophylaxis (ASAP) trial

Trisha Peel,[1,2] Sarah Astbury,[1] Allen C Cheng,[2,3] David Paterson,[4,5] Kirsty Buising,[6,7] Tim Spelman,[8] An Tran-Duy ,[9] Richard S de Steiger,[10,11] on behalf of the ASAP Trial Group

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For numbered affiliations see end of article.

Correspondence to
Dr Trisha Peel;
Trisha.Peel@monash.edu

ABSTRACT

Introduction Resistant Gram-positive organisms, such as methicillin-resistant staphylococci, account for a significant proportion of infections following joint replacement surgery. Current surgical antimicrobial prophylaxis guidelines recommend the use of first-generation or second-generation cephalosporin antibiotics, such as cefazolin. Cefazolin, however, does not prevent infections due to these resistant organisms; therefore, new prevention strategies need to be examined. One proposed strategy is to combine a glycopeptide antibiotic with cefazolin for prophylaxis. The clinical benefit and cost-effectiveness of this combination therapy compared with usual therapy, however, have not been established.

Methods and analysis This randomised, double-blind, parallel, superiority, placebo-controlled, phase 4 trial will compare the incidence of all surgical site infections (SSIs) including superficial, deep and organ/space (prosthetic joint) infections, safety and cost-effectiveness of surgical prophylaxis with cefazolin *plus* vancomycin to that with cefazolin *plus* placebo. The study will be performed in patients undergoing joint replacement surgery. In the microbiological sub-studies, we will examine the incidence of SSIs in participants with preoperative staphylococci colonisation (Sub-Study 1) and incidence of VRE acquisition (Sub-Study 2). The trial will recruit 4450 participants over a 4-year period across 13 orthopaedic centres in Australia. The primary outcome is the incidence of SSI at 90 days post index surgery. Secondary outcomes include the incidence of SSI according to joint and microorganism and other healthcare associated infections. Safety endpoints include the incidence of acute kidney injury, hypersensitivity reactions and all-cause mortality. The primary and secondary analysis will be a modified intention-to-treat analysis consisting of all randomised participants who undergo eligible surgery. We will also perform a per-protocol analysis.

Ethics and dissemination The study protocol was reviewed and approved by The Alfred Hospital Human Research Ethics Committee (HREC/18/Alfred/102) on 9 July 2018. Study findings will be disseminated in the printed media, and learnt forums.

Trial registration number ACTRN12618000642280

Strengths and limitations of this study

- Pragmatic trial conducted in the 'real-world' setting comparing combination prophylaxis with vancomycin and cefazolin to current standard care with cefazolin prophylaxis alone.
- Recruiting from a broad-range of orthopaedics centres including large, metropolitan, tertiary public and private hospitals and regional hospitals.
- Examines clinical and economical efficacy of combination prophylaxis, in addition to examining the microbiological impact of broader prophylaxis.
- Targets all patients undergoing joint replacement surgery, rather than 'high-risk' groups.

INTRODUCTION

Over 121 000 joint replacement (arthroplasty) procedures were performed in Australia in 2018.[1] The demand for this surgery will double over the coming decade.[1–4] A devastating complication of joint replacement surgery is surgical site infections (SSIs), which occurs in up to 6% of surgeries.[5–12] Of concern, the rate of SSIs is increasing relative to the number of procedures performed.[2 13] These infections are associated with significant patient morbidity in addition to a five-fold increase in mortality.[14 15] There is also a significant ecological impact associated with the prolonged antimicrobial therapy required to treat these infections.[16–18] SSIs place a substantial economic burden on the healthcare system.[19–21]

Resistant Gram-positive organisms are the most common cause of SSIs following joint replacement surgery in Australia and are associated with poorer outcomes.[14 22–24] These resistant Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), other methicillin-resistant *Staphylococcus* species and *Enterococcus* species, cause over 50% of all culture-positive infections in Australia, which is similar to international reports.[22 25–33]

Surgical antimicrobial prophylaxis with a beta-lactam antimicrobial, such as cefazolin, is the mainstay of SSI prevention. However, current guidelines are informed by research undertaken over 30 years ago when methicillin-sensitive *Staphylococcus aureus* was the predominant organism.[34–36] Over time, there has been an increased incidence of antimicrobial resistant organisms and these data are not reflective of the current ecology.[22 33 37–39]

Glycopeptides are bactericidal antimicrobials that inhibit cell wall synthesis and have broad activity against Gram-positive organisms, including MRSA and other methicillin-resistant staphylococci including methicillin-resistant *Staphylococcus epidermidis*. The national guidelines (Australian Therapeutic Guidelines: Antibiotic)[40] recommend glycopeptides for surgical antimicrobial prophylaxis; however, the indication for use is limited to patients with immediate beta lactam hypersensitivity or known MRSA colonisation or infection.

These traditional risk factors for MRSA and for glycopeptide antibiotic surgical antimicrobial prophylaxis are losing relevance, given over 20% of community acquired *Staphylococcus aureus* is methicillin resistant and this proportion is increasing.[33 39] Furthermore, risk factors for the acquisition of methicillin-resistant coagulase-negative staphylococci and enterococci SSIs, are poorly delineated.

One proposed prevention strategy is to add glycopeptide antibiotics to the beta-lactam surgical antimicrobial prophylaxis (henceforth referred to as '*combination prophylaxis*'). International guidelines suggest adoption of combination prophylaxis if the MRSA prevalence exceeds 10%, considered by expert consensus to represent a 'high' rate.[35 39 41] However, the benefit and risks of this strategy have been poorly examined.[29 35 42–44] Of importance, single agent glycopeptide surgical antimicrobial prophylaxis is not recommended (except in immediate beta-lactam hypersensitivity) due to the observed increase in methicillin-sensitive *Staphylococcus aureus* following use of single agent glycopeptide surgical antimicrobial prophylaxis.[31 45] To date there is a paucity of randomised controlled trials (RCTs) examining combination prophylaxis in joint replacement surgery.

A systematic review and meta-analysis was performed by Saleh and colleagues comparing glycopeptide and beta-lactam surgical antibiotic prophylaxis in cardiovascular and orthopaedic surgery.[46] Overall 14 RCTs were included in the meta-analysis with six studies examining patients undergoing orthopaedic procedures. No included trial examined prophylaxis with beta-lactam and glycopeptide combinations.[46]

There is emerging evidence from cohort studies demonstrating a reduction in the incidence of SSIs after introduction of combination prophylaxis.[30 44 47–49] In particular, large cohort studies by Sewick *et al* and Liu *et al* reported a reduction in the incidence of SSIs isolating resistant Gram-positive organisms following adoption of combination prophylaxis with vancomycin and cefazolin.[48 50] Similarly, Tornero *et* al reported a 64% reduction in the overall rate of prosthetic joint infection following the adoption combination prophylaxis with teicoplanin and cefuroxime (1.26% *vs* 3.51%; p=0.002); of note, there was a significant reduction in all *Staphylococcus aureus* SSIs (methicillin resistant and sensitive) in the combination prophylaxis cohort (0 *vs* 21 SSIs; p=0.0001).[30] This suggests a potential synergy between glycopeptides and beta-lactams, which is corroborated by other laboratory and clinical studies.[51 52] Reineke *et al* conducted a before and after study in cardiac surgery patients (n=3902). This study examined the addition of vancomycin to surgical prophylaxis with cefuroxime for 'high-risk' patients (n=1493). High-risk patients included; body mass index <18 or >30 kg/m^2, reoperation, stage 5 chronic kidney disease, insulin-dependent diabetes mellitus, severe or very severe chronic obstructive pulmonary disease or administration of immunosuppressive medication.[49] In the high-risk patients, the addition of vancomycin to surgical antimicrobial prophylaxis was associated with a reduction in SSI from 8.6% to 3.8% (OR 0.43; 95% CI 0.27 to 0.67; p<0.001). In the overall cohort, when correcting for risk status, the addition of vancomycin was associated with a 70% reduction in the odds of SSI (OR 0.30; 95% CI 0.14 to 0.62; p=0.001).

The reduction in SSI incidence and hence cost savings must be balanced against the potential unintended consequences and the associated costs incurred in patients receiving combination prophylaxis. These concerns include serious adverse outcomes such as acute kidney injury, reported by Courtney *et al* following the introduction of combination prophylaxis (13% vs 8% for cefazolin surgical antimicrobial prophylaxis; p=0.002).[53] Another concern is the potential for promotion of glycopeptide resistance among local pathogens.[54] Exposure to glycopeptides has been linked with colonisation with organisms such as vancomycin-resistant *Enterococcus* (VRE).[55] This risk of VRE colonisation or the emergence of other antimicrobial resistance following combination prophylaxis has not been established.[47 48 54 56–58]

Therefore, clinical equipoise exists about the use of combination prophylaxis, given its increased efficacy as well as the potential downstream consequences of broad-spectrum antimicrobial use. Although it is currently unclear whether the benefit of combination prophylaxis outweighs the potential harm, glycopeptide antibiotics have been incorporated into surgical antimicrobial prophylaxis protocols in many local and international centres.[29 31 44 59] Given the high volume of joint replacement surgery, surgical antimicrobial prophylaxis contributes to a large amount of antimicrobial consumption

and may exert ecological pressure on microorganisms.[59] Increasing antimicrobial resistance is one of the top five global public health issues identified by the WHO.[60] There is a strong imperative to ensure judicious, evidence-informed use of antibiotics, avoiding unnecessary overuse, to conserve this important resource.

The Australian Surgical Antibiotic Prophylaxis (ASAP) trial will compare the incidence of SSI, safety and cost-effectiveness of surgical prophylaxis with cefazolin *plus* vancomycin to that of cefazolin *plus* placebo in patients undergoing elective or expedited joint replacement surgery.

METHODS AND ANALYSIS

Trial design

This is a double-blind, parallel, placebo, superiority, phase 4, randomised controlled trial comparing cefazolin plus vancomycin (intervention arm) to cefazolin plus normal saline placebo (standard arm) surgical antimicrobial prophylaxis for the prevention of all SSIs (superficial, deep and organ/space) in patients undergoing elective or expedited replacement surgery procedures. The study will be constructed and reported in accordance with the Consolidated Standards of Reporting Trials statement and the Standard Protocol Items: Recommendations for Interventional Trials guidelines.[61 62]

Patient and public involvement

Patients were not involved in the design of this research project.

Study setting

The study population will be drawn from patients scheduled for elective or expedited joint replacement procedures at participating centres in Australia.

Eligibility criteria

Inclusion criteria

Patients ≥18 years of age undergoing elective or expedited joint replacement surgery

Exclusion criteria

Hypersensitivity to either cefazolin or glycopeptides, pregnancy and lactating women, surgery for suspected or proven SSI, emergency or time critical surgery including arthroplasty for management of trauma/fracture including fractured neck of femur and, arthroplasty for bone/soft tissue tumour, return to theatre/redo operation within index admission, documented or suspected infection or colonisation with MRSA (this does not include patients with MRSA detected for the Microbiological Sub-Study *see below*).

Interventions

Cefazolin surgical antimicrobial prophylaxis

All enrolled patients will receive cefazolin. The dosage, administration and timing of cefazolin surgical antimicrobial prophylaxis will be in keeping with the Australian Therapeutic Guidelines: Antibiotics.[40]

Vancomycin/placebo surgical antimicrobial prophylaxis

Vancomycin/placebo will be prepared and delivered by PCI Clinical Services (PCI) to the pharmacy department or nominated personnel of the involved centres. Active treatment will consist of 1.5 g vancomycin supplied as three vials of 500 mg vancomycin in a carton. PCI will remove the commercial labels and place a sheath over the vial. Placebo will consist matching empty vials with a matching sheath in the carton. At the time of index surgery, the anaesthetist or nurse will reconstitute the three vials in keeping with product information and/or local guidelines. In participants weighing less than 50 kg, two vials (out of the three vials) will be reconstituted (yielding a dose of 1000 mg vancomycin in the active arm). Vancomycin/placebo will be infused ideally at a rate of 10 mg/min. In patients who are closely monitored, higher rates of infusion may be used, and the rate slowed if clinically significant hypotension occurs.[40] The infusion will commence up to 120 min prior to incision and the infusion may be completed after incision.[40 63] No postoperative dose will be administered. All vials will be discarded after use as per local hospital processes.

In the event of a hypersensitivity reaction, the randomisation code can be broken by contacting the Monash Department of Infectious Diseases Research Office to allow emergency unblinding. The reason for code breaking will be recorded and this information will be forwarded to the Project Steering Committee and Data Safety Monitoring Committee.

Staphylococcus carriage sub-study

As an *a priori* subgroup analysis, the impact of immediate staphylococcal perioperative carriage on SSIs incidence will be assessed. To determine the prevalence of immediate perioperative carriage of *Staphylococcus aureus* and coagulase-negative staphylococci, participants will undergo screening for *Staphylococcus* at preadmission clinic with swabs from the anterior nares and perineum.[64] One swab will be collected at each site (total of two swabs). Results from the preadmission joint replacement procedure screening swab will not influence the study exclusion or allocation. Information pertaining to the methods for collection, processing, evaluation and storage of biological specimens are outlined in the Department of Infectious Diseases, Clinical Trial Microbiology Laboratory Procedure Manual (a separate protocol will be published for the Staphylococcus carriage sub-study).

Vancomycin-resistant enterococci sub-study

To determine the ecological impact of combination prophylaxis, a sub-study will be performed at a single centre. Participants in this subgroup will undergo screening for VRE colonisation with perineal swabs, performed at four study intervals (two swabs collected at each time point, total of eight swabs): (i) preadmission

clinic, (ii) postoperatively on day 3, (iii) day 14 and (iv) day 30 following the joint replacement procedure. Acquisition of VRE is defined as the occurrence of positive surveillance swab by day 30 following the index joint replacement procedure in a patient with previously negative preadmission surveillance swab. Information pertaining to the methods for collection, processing, evaluation and storage of biological specimens are outlined in the Laboratory Procedure Manual (a separate protocol will be published for the VRE sub-study).

Outcomes

Primary outcome

The primary endpoint for this trial is a composite endpoint comprised of the incidence of all SSIs (superficial incisional, deep and organ/space SSI) at 90 days following operation defined according to Centers for Disease Control and Prevention (CDC) definitions.[65]

Secondary outcomes

Incidence of superficial and deep SSI, incidence of late SSI occurring between 90 to 180 days post index procedure, incidence of SSI due to specific microorganism(s): *Staphylococcus aureus* (methicillin resistant and methicillin susceptible); coagulase-negative *Staphylococcus* species (methicillin resistant and methicillin susceptible); *Enterococcus* species; Other Gram-positive organisms; Gram-negative organisms and/or; fungi, incidence of SSI according to procedure, incidence of other healthcare-associated infections defined according to CDC Healthcare Associated Infection (HCAI) Control Practices Advisory Committee[66–68] including: hospital acquired pneumonia, urinary tract infections, blood stream infections and/or *Clostridium difficile* infection.

Microbiological sub-study outcomes

Incidence of SSI in patients colonised with *Staphylococcus* species and, incidence of VRE acquisition.

Adverse events outcomes

Incidence of adverse events including: acute kidney injury, hypersensitivity reactions and all-cause mortality.

Health-economic outcomes

Direct healthcare costs based on resource utilisation, quality of life using the EuroQoL instrument (EQ-5D-3L) and incremental cost-effectiveness ratios of the combination prophylaxis compared with cefazolin alone.

Clinical outcome verification

In participants meeting the criteria for SSI, secondary outcomes of interest or adverse events outcomes, de-identified data will be forwarded to the ASAP Clinical Trial Coordinator for endpoint adjudication. This de-identified data will be collated by the ASAP Clinical Trial Coordinator for review and adjudication by the blinded Outcomes Verification Panel comprising the ASAP Clinical Trial Coordinator and two investigators. Ascertainment of outcomes will be undertaken according to review against strict criteria. Outcomes will be confirmed based on agreement by the majority of Panel members. In the event of lack of agreement between the Panel, a third investigator will adjudicate.

Participant timeline

The planned study duration is 4 years. Participants will be followed for 180 days to capture all relevant clinical and health economic outcomes. Assessment for SSIs will extend to day 180 as a secondary outcome, however attribution of cause of these 'late' infections to microorganisms acquired in the perioperative period (and therefore potentially influenced by the surgical antimicrobial prophylaxis administered) is unclear.

Sample size

The estimated sample size required in each of the two (equally-sized) groups is 2115 resulting in a total sample of 4230 based on the following: (i) alpha=0.05, two-sided; (ii) power=90%; (iii) expected rates of SSI (superficial incisional and deep infection) 5.0% for standard care arm and 3.0% for intervention arm. Allowing for a lost to follow-up rate of 5%, the trial will recruit 4450 participants in total. The sample size calculation is based on the most relevant data, powered to cover a range of the most probable and realistic effect sizes, and includes: an incidence of SSIs (superficial incisional and deep infection) of 5% and incidence of resistant Gram-positive organisms based on local and international data of 50%.[10–12 20 22 28 32 69 70] Based on current large cohort studies, combination prophylaxis reduced the proportion of resistant Gram-positive organisms by >80%.[48 50] Assuming the effect is limited to these organisms, it was estimated that combination prophylaxis will reduce the rate of resistant Gram-positive organisms from 50% to 10% and the overall proportion of SSIs 5.0% transmuted to 3.0%. This absolute risk reduction (2.0%) is more conservative than the absolute risk reduction reported by Tornero *et al* (2.25%)[30] and Reineke *et al* (2.9%).[49]

Recruitment

Patients waitlisted for elective or expedited joint replacement procedures will be assessed for eligibility for the study prior to planned index surgery. Eligible participants will be approached by the designated study personnel. The designated study personnel will provide a verbal outline of the project which will detail the nature of the study and commitment required in addition to provision of a plain language statement. In those participants willing to proceed, informed written consent will be obtained by the designated study personnel and the participant will be assigned a unique study number.

Randomisation

Following informed consent, randomisation will be performed at the individual patient level. Participants will be randomly assigned in a ratio of 1:1 to either the standard care arm or the intervention arm. Randomisation of participants to treatment arms will be as

a password-protected, secure website using a central, computer-based randomisation programme with permutated blocks and allocation of participants stratified according to the centre and by procedure. The treating clinicians and study investigators will have no role in the assignment process.

Blinding

Participants, treating clinicians, all members of the research team including the study statistician will be blinded to treatment arm allocation.

Data management

The processes for identifying outcomes will be conducted by the project research officer who will collect demographic data, results from serum urea, electrolytes and creatinine, full blood examination and other laboratory testing, *Staphylococcus* and VRE screening swabs (*substudy participants only*), operative data and quality of life (EQ-5D-3L). Active surveillance conducted by the site research staff will comprise the following:

- Review of all participants' medical records on discharge and follow-up at clinic.
- Retrieval and review of records from other healthcare institutions as required.
- Telephone contact for outcomes at 30, 90 and 180 days following index surgery.
- Linkage with the Department of Health Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Schedule (PBS) data.

Following completion of the paper-based case report form, data will need to be entered by research staff to the trial database (Research Path) through a web-based secure data entry system.

Statistical methods

Analysis for primary outcome

The analysis plan will be finalised prior to completion of recruitment. The primary analysis will be a modified intention-to-treat (mITT) analysis. The mITT population will consist of all randomised participants who undergo eligible arthroplasty surgery. Participants will be analysed according to the group to which they were randomised, whether they receive study drug or not. We will also perform a per-protocol analysis which will include participants who completed the treatment to which they were allocated, meaning *only* those patients who receive all doses of study drug or placebo according to their original randomised allocation. As a large randomised controlled trial, covariate balance is expected. The primary outcome will be compared between the two groups through calculation of the relative risk and risk difference. A test of interaction will be used to assess for sub-group effects.

Analysis for secondary outcomes and safety outcomes

Secondary outcome measures will be compared between groups using Kaplan-Meier estimates and HRs for time to event data, relative risk, exact methods or OR, dependent on the frequency of event and for categorical outcomes and Student's t-test or rank sum test as appropriate for continuous data. If the patient characteristics are not perfectly balanced between the two treatment arms, Cox proportional hazard models will be used to adjust the intervention effect on the event rates for potential cofounders. Overall regression model fit to the observed data will be assessed using the Hosmer-Lemeshow X^2 statistic. Safety population will include all participants who received doses of study drug or placebo including those that did not have surgery (for example in the event of surgery cancellation). Poisson modelling will be used to directly calculate the relative risk of acute kidney injury and model fit will be assessed using X^2 goodness of fit test for a Poisson distribution. In the event that the count data is over-dispersed, then a negative binominal or zero-inflated models will be used as appropriate.

Health economic analysis

Health economic analysis will be a stand-alone substudy conducted from a healthcare perspective. The main outcome of interest in the economic evaluation is incremental cost-effectiveness ratios in terms of net costs per unit of health gain. Net costs will comprise the costs of combination prophylaxis minus costs saved from the reduction in downstream health services utilisation, which will be obtained from administrative data from the hospital sites including medical (surgical and non-surgical), nursing, pathology, pharmacy, theatre, rehabilitation and allied health costs. MBS and PBS data will be linked to capture impact in participants' broader health service utilisation. All costs will be adjusted for inflation using Australian Bureau of Statistics consumer price indices and discounted at 5% to account for price changes and time preference respectively. The cost-effectiveness analysis will calculate the incremental cost per SSI avoided by using combination prophylaxis compared with standard care. We will also estimate incremental cost per life year gained and per quality-adjusted life years gained to undertake cost-utility analysis. Uncertainty will be assessed by bootstrapping and developing CIs for all key results. Extensive one-way and probabilistic (Monte Carlo) sensitivity analyses will be undertaken to understand the impact of uncertainty on results.[71] Final results will be presented using cost-effectiveness planes and acceptability curves.

Interim analysis

Interim analysis will consider the defined study and safety endpoints after enrolment of 2000 patients. Early stopping will be considered based on O'Brien Fleming stopping limits calculated using the Lan-DeMets approach.[72] Results will be made available to the Data and Safety Monitoring Committee (DSMC). The DSMC will discuss the interim results and vote for continuation or stopping the trial. A majority vote to stop the trial will be communicated to the Steering Committee at the Trial Coordinating Centre according to predetermined stopping rules and consideration of other relevant evidence.

Data monitoring

Random audits of centres will be undertaken, to assess the accuracy and legitimacy of the trial data. Statistical monitoring of the data completeness, data variance and risk-appropriate endpoint rates will be done for all patient data.

Adverse events monitoring

The trial drug will be given in the perioperative period as a dose prior to skin incision. Serious adverse events (SAEs) will be reported to the sponsor within 24 hours of sites being notified. SAE and other safety data will be reviewed by the DSMC.

Data and safety monitoring committee

In addition to reviewing the results of the interim analysis, the DSMC will act in an advisory capacity to monitor data quality, primary and secondary endpoint evaluation and study progress. The DSMC will consider adverse events and events concerning to the Investigators. Reporting of SAE's to Research Governance Office (RGO)/Executive Committees for the specific study site will either be submitted individually at the time of the SAE or as a line listing report annually at the discrepancy of the individual site RGO/Executive Office.

ETHICS AND DISSEMINATION

Ethics and consent

This study will be conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research. The protocol for this study has been submitted to all involved university and participating hospital Human Research Ethics committees (HREC) for assessment and approval. Participant recruitment will not commence until approval by the Institutional/Hospital HREC committee has been obtained.

The investigators plan to publish the results in a peer-reviewed journal. All planned publications arising from this project will be submitted to Project Steering Committee for consideration and authorisation. Members of the ASAP Trial Group will be potentially eligible for authorship on any publications arising from the study. Any planned publication arising from this research project must first be reviewed and agreed on by the Project Steering Committee. Criteria for authorship will be in keeping with the International Committee of Medical Journal Editors.[73]

DISCUSSION

Joint replacement surgery is high volume and expensive surgery, with demand set to double over the next decade. Resistant Gram-positive organisms are a major cause of SSIs however, the benefit of preventative strategies such as combination surgical antimicrobial prophylaxis (SAP) has not been established and must be balanced against the potential negative consequences of broader-spectrum antimicrobial therapy. The emergence of antimicrobial resistance is a major health issue faced by Australia and globally.

This pragmatic, phase 4 study will examine the potential additive benefit of vancomycin and is the first randomised controlled trial to examine the clinical, microbiological and economical impact of combination surgical antimicrobial prophylaxis in joint replacement surgery. There are a number of agents with anti-MRSA activity in addition to glycopeptides (linezolid, daptomycin, ceftaroline) however, there is limited data on the efficacy of these agents for surgical antimicrobial prophylaxis. Given vancomycin is currently approved and administered for surgical antimicrobial prophylaxis, with significant clinical experience with the use of this antibiotic, the results of this trial will be immediately translatable and will inform other surgery disciplines.

Author affiliations
[1]Infectious Diseases, Monash University, Melbourne, Victoria, Australia
[2]Infectious Diseases Unit, Alfred Hospital, Melbourne, Victoria, Australia
[3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[4]Centre for Clinical Research, University of Queensland, Brisbane, Queensland, Australia
[5]Infectious Diseases, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia
[6]Medicine, University of Melbourne, Melbourne, Victoria, Australia
[7]Victorian Infectious Diseases Service, Royal Melbourne Hospital, Melbourne, Victoria, Australia
[8]Department of Surgery, St Vincent's Hospital, The University of Melbourne, Melbourne, Victoria, Australia
[9]Centre for Health Policy, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia
[10]Surgery, The University of Melbourne, Melbourne, Victoria, Australia
[11]Orthopaedics, Epworth HealthCare, Richmond, Victoria, Australia

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Collaborators The ASAP Trial Group Principal Investigator: Dr Trisha Peel. The ASAP Trial Group Co-Investigators: Professor Peter Choong, Professor Allen Cheng, Professor David Paterson, Assistant Professor Kirsty Buising, Assistant Professor Michelle Dowsey, Professor Ross Crawford, Professor Richard de Steiger. Statistician: Dr Tim Spelman. Health Economists: Professor Philip Clarke, Dr An Tran-Duy. Associate Investigators: Professor Ben Howden, Dr Peter Rehfisch, Dr Robert Molnar. Site Principal Investigators: Dr Sam Adie, Mr Glenn Boyce, Dr Catherine McDougall, Dr Jonathon Mulford, Dr Michael Solomon. ASAP Trial Coordination and Administration: Ms Sarah Astbury (ASAP Clinical Trial Coordinator), Ms Tiffany Harris-Brown, Ms Janine Roney. Department of Infectious Diseases Microbiology Laboratory: Professor Anton Peleg, Dr Jessica Wisniewski, Ms Stephanie Pereira, Ms Zweena Badoordeen.

Contributors TP: Initial trial concept, funding application, trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. SA: Trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. ACC: Initial trial concept, funding application, trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. DP: Initial trial concept, funding application, trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. KLB: Initial trial concept, funding application, trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. TS: Initial trial concept,

funding application, trial design including statistical analysis plan, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. ATD: Trial design including health economic analysis plan, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work. RdS: Initial trial concept, funding application, trial design, manuscript production and editing, final approval of the version to be published, agreement to be accountable for all aspects of the work.

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Patient consent for publication Not required.

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ORCID iD

An Tran-Duy http://orcid.org/0000-0003-0224-2858

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