Study protocol for PREPARE: a phase II feasibility/safety randomised controlled trial on PeRiopErative Penicillin AlleRgy TEsting

BMJ Open

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ABSTRACT

Introduction Patient-reported antibiotic allergy labels (AALs) are common. These labels have been demonstrated to have a negative impact on use of appropriate antibiotics and patient-related health outcomes. These patients are more likely to receive suboptimal antibiotics, have increased rates of surgical site infections and are more likely to be colonised with multidrug-resistant organisms. Increasing recognition that antibiotic allergy forms a key part of good antimicrobial stewardship has led to calls for greater access to antibiotic allergy assessment. PREPARE is a pilot randomised controlled trial of beta-lactam allergy assessment and point of care delabelling in perioperative patients utilising a validated antibiotic allergy assessment tool that has been repurposed into a smartphone application. The aim of the study is to assess the feasibility and safety of this approach in the perioperative outpatient setting.

Methods and analysis Adult participants requiring elective surgery and are likely to require prophylactic intravenous antibiotics will be recruited. During the intervention phase, participants will be randomised to the intervention or control arm, with control patients receiving usual standard of care. Those randomised to intervention undertake a risk assessment via the smartphone application, with those deemed low risk proceeding to direct oral provocation with either a penicillin or cephalosporin. Study outcomes will be evaluated in the postintervention phase, 30 and 90 days after surgery.

Feasibility of intervention delivery and recruitment will be reported as proportions with respective 95% CIs. Participants who experience an antibiotic adverse event will be reported by group with respective 95% CIs and compared using modified Poisson regression model with robust SE estimation.

Ethics and dissemination This protocol has received approval from the Austin Health human research and ethics committee, Heidelberg, Victoria, Australia (HREC/17/Austin/575). Results will be disseminated via publication in peer-reviewed journals as well as presentation at international conferences.

Trial registration number ACTRN12620001295932.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The impact of beta-lactam allergy assessment and delabelling in perioperative medicine on patient and outcomes via controlled studies is absent.
⇒ If successful, this study will form the foundation for a larger randomised controlled trial to be conducted to assess these impacts on a range of clinical outcomes.
⇒ Beta-lactam allergy assessment remains a finite resource, broadening out delabelling efforts to non-allergy settings would allow significant upscaling.
⇒ As this is a pilot study examining feasibility and safety outcomes, it is not sufficiently powered to assess the impact of delabelling on health outcomes.
⇒ Due to the nature of antibiotic allergy delabelling, the study can only be partially blinded as patients are delabelled prior to surgery in the intervention arm.

INTRODUCTION

Up to one in four Australians and North Americans admitted to hospital have a patient-reported antibiotic allergy (so-called antibiotic allergy labels (AALs)).[1] These reported AALs impact antibiotic prescribing, antibiotic appropriateness and patient outcomes.[1 2] We have demonstrated that clinicians, pharmacists and allergists poorly understand the concepts of antibiotic cross reactivity, in particular which beta-lactam antibiotics are safe to employ in patients with penicillin 'allergy'.[3 4] Our group, along with others, demonstrated the burden, impact and severity of antibiotic allergy demonstrating significant knowledge gaps in antibiotic allergy and the potential utility of point of care assessment tools.[1 3–5] In particular, a validated antibiotic allergy assessment tool has been deployed in health services studies to improve accuracy of assessment and delabelling.[6–8] AALs can

have a significant impact on antimicrobial stewardship and medication safety, with the recent Infectious Diseases Society of America and Australian Antimicrobial stewardship guidelines calling for greater access to antibiotic allergy assessment and testing.[9 10]

AALs carry significant negative implications for patients and health services. Patients with AALs are more likely to receive suboptimal antibiotics, be colonised with multidrug-resistant organisms, develop *Clostridium difficile* diarrhoea and experience surgical site infections.[11–15] These patients are also more likely to require intensive care unit admission and have a higher inpatient mortality.[16] Antibiotic allergy delabelling, the removal of AALs following antibiotic allergy testing, has been demonstrated to be safe and effective, in both immunocompetent and immunocompromised cohorts.[17 18] Pilot data from non-randomised and retrospective cohort studies demonstrate that delabelling of penicillin AALs in the perioperative period is associated with improved antibiotic utilisation.[19 20] However, an assessment of the impact of point-of-care assessment and delabelling in perioperative medicine on patient and healthcare outcomes via prospective controlled studies remains absent.

PREPARE is an enhanced beta-lactam assessment and point-of-care delabelling feasibility and safety study utilising a validated Antibiotic Allergy Assessment Tool that has been adapted into a smart phone application.[8] Following risk stratification via the app in the preoperative anaesthetic clinic, a direct oral beta-lactam provocation protocol is activated which enables delabelling in those randomised to the intervention group. Previously, clinician education antibiotic allergy programmes and protocols have improved antibiotic prescribing and beta-lactam uptake in those with a reported antibiotic allergy in perioperative medicine.[21 22] This phase II multicentre randomised controlled trial study builds on this literature and robust pilot oral antibiotic provocation data and assessment tools, by evaluating the feasibility and safety of a point of care assessment tool and oral provocation programme in the perioperative care of elective surgical patients and explores the impacts on appropriate antibiotic utilisation. While assessment tools for antibiotic allergy are available,[8 23] their utility in a decision support point of care system (eg, smartphone application) is unknown.

We hypothesise that antibiotic allergy assessment and point-of-care beta-lactam provocation in the perioperative setting for elective surgery is feasible and safe. Further, we aim to estimate the magnitude of potential effect for further progression to an efficacy or effectiveness study. The aim of the trial is to improve antibiotic appropriateness and increase beta-lactam uptake, in particular penicillins and cephalosporins, in patients that are labelled as 'penicillin or cephalosporin allergic' and undergoing elective surgery. We aim to develop and assess the feasibility and safety of a point of care antibiotic allergy toolkit in the perioperative clinic, and secondarily explore the

impact on subsequent antibiotic utilisation, surgical site infections and patient outcomes.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES
Patient and public involvement statement
No patient involvement.

This is a multicentre phase II feasibility, safety and acceptability randomised controlled trial that will be undertaken within the outpatient presurgical anaesthetic clinics of Austin Health (Melbourne, Victoria, Australia), Royal Melbourne Hospital (Melbourne, Victoria, Australia) and Alfred Hospital (Melbourne, Victoria, Australia). The study is planned to run from 14 December 2020 through to 31 March 2023. An overview of the study has been summarised in figure 1. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). Summary of trial registration data can be found in table 1. The protocol report was prepared as per Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[24]
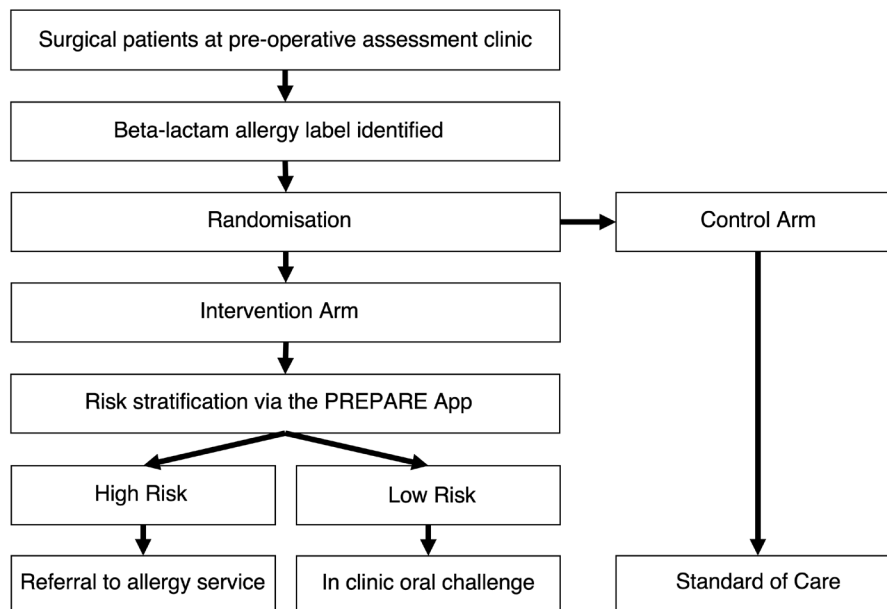
Participants
Adult patients (≥18 years old) will be included in the study if they are reviewed in the perioperative assessment clinic under the care of a surgical and/or anaesthetic unit, have a reported AAL and will likely require intravenous antibiotic therapy in planned perioperative care. Participants will be excluded if (1) they are currently receiving inpatient care; (2) are under the care of an allergy/immunology specialist or have previously been referred to or assessed by a specialist for beta-lactam allergy; (3) patients currently receiving beta-lactam antibiotic therapy; (4) require only non-beta-lactam antibiotics for an infection or colonisation with an organism resistant to beta-lactam (eg, methicillin-resistant *Staphylococcus aureus*, extended spectrum beta-lactamase producing gram negatives); (5) are patients undergoing emergency and/or trauma surgery; (6) are contraindicated for oral antibiotic provocation; (7) are receiving treatment that may interfere with provocation challenge, eg >10 mg prednisolone or equivalent daily,[7] receiving antihistamine therapies; (8) any history of drug-associated anaphylaxis or idiopathic urticaria/anaphylaxis.

Interventions
This study will have two phases: intervention phase and postintervention evaluation.

Baseline education will be provided to all perioperative clinicians (anaesthetists) prior to study commencement. Routine care will be provided by the treating perioperative physician and if randomised to the intervention, the clinician will perform the enhanced allergy assessment (utilising a risk stratification decision support smartphone app) and subsequent point-of-care oral beta-lactam provocation for low-risk beta-lactam allergies will be carried out by study investigators, preferably within the anaesthetic clinic structure. During the first step of the

Figure 1 Study overview.

intervention arm, participants receive an enhanced antibiotic allergy assessment and are assigned a '**risk score**' (low, moderate or high) and allergy '**type**' based on a validated and adapted Antibiotic Allergy Assessment Tool.[8] Recommendations will then be generated depending on the risk stratification (see figure 2 for details). Based on this assessment, participants will receive approval for point-of-care oral beta-lactam provocation if found to be 'low risk' (white or green on assessment tool, see table 2).

Drug provocation will occur in a supervised clinic environment with a single dose of oral amoxicillin 250 mg, penicillin VK 250 mg if the specific index penicillin is known or cephalexin 250 mg in the context of a cephalosporin allergy label. If the allergy label is to an unspecified penicillin or to a penicillin with no oral formulation, amoxicillin 250 mg will be utilised. Once provocation dose is administered, routine observations will be performed for 1 hour post oral provocation. Examples of a positive reaction include rash, urticaria, angioedema, hoarse voice or hypotension. If a reaction occurs, the participant will be appropriately managed as per local hospital protocols. This will be reported as an adverse event (AE) as per protocol and the allergy will be reinstated and/or reinforced in the medical record.

If no reaction on oral provocation occurs, participants will be informed that their AAL has been delabelled and are provided with information on how to contact the research team if a delayed reaction were to occur. In the case of provocation for a penicillin allergy label where no oral formulation exists (eg, piperacillin-tazobactam), the specific allergy label will be maintained but tolerance of amoxicillin will be noted. The research team will also contact the participant 5 days post oral provocation to check for a delayed positive provocation test. The AAL is subsequently removed from the medical record

(if appropriate), and a letter generated and sent to the participant and their general practitioner.

A recommendation for operative antibiotic utilisation will subsequently be generated. The non-intervention arm will receive routine standard of care by the perioperative physician. No participants in the standard of care arm will receive an enhanced antibiotic allergy assessment or point-of-care oral beta-lactam provocation.

The postintervention evaluation stage will assess the degree to which the intervention is delivered as intended (also known as implementation fidelity) in comparison with the published protocol.[25 26] This will be examined through data collection on adherence to the components of the bundle and quality and complexity of delivery of the intervention. We will also examine the feasibility and mechanisms for data collection for the clinical outcome measures.

Outcomes

This study has two primary outcomes: to determine the feasibility of intervention delivery (defined as the proportion of patients randomised to the intervention arm who had the intervention delivered as per protocol) and feasibility of recruitment defined as the proportion of patients consenting to participation in the study as per protocol from eligible patients; and to assess the safety of the protocol by the proportion of patients with a beta-lactam allergy who experience an antibiotic-associated AE and/or severe adverse drug reaction as per protocol definitions. Secondary outcome measures have been summarised in box 1 but include: (1) the proportion of patients with a beta-lactam allergy where a guideline-preferred beta-lactam antibiotic is used for antibiotic prophylaxis; (2) proportion of patients with a beta-lactam allergy that receive any beta-lactam as surgical prophylaxis and receive any beta-lactam in the postoperative

Table 1 Trial registration data

Data category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry, anzctr.org.au ACTRN12620001295932
Date of registration in primary registry	30 November 2020
Secondary identifying numbers	N/A
Source(s) of monetary or material support	Merck Sharp & Dohme
Primary sponsor	Merck Sharp & Dohme
Secondary sponsor(s)	N/A
Contact for public queries	Dr Joseph F De Luca, BSc (Mol Biol) MBBS MPHTM FRACP (joseph.deluca@austin.org.au)
Contact for scientific queries	Dr Joseph F De Luca, BSc (Mol Biol) MBBS MPHTM FRACP Centre for Antibiotic Allergy and Research, Melbourne Australia
Public title	Streamlining antibiotic allergy testing for elective surgery patients using smartphone-based apps.
Scientific title	PeRiopErative Penicillin/Cephalosporin AlleRgy TEsting: a phase II feasibility/safety randomised controlled trial to empower anaesthetists to risk stratify and delabel antibiotic allergy labels in the perioperative period using digital health solutions.
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Penicillin allergy, cephalosporin allergy, antibiotic allergy
Intervention(s)	Intervention: risk assessment by perioperative clinician via a smartphone app, followed by allergy testing or antibiotic challenge.
	Control: standard of care
Key inclusion and exclusion criteria	Inclusion criteria: reported penicillin or cephalosporin allergy, expected to require intravenous antibiotic therapy in planned perioperative care.
	Exclusion criteria: inpatients, age <18 years, patients currently receiving beta-lactam antibiotic therapy, previous referral or assessment by a specialist for beta-lactam allergy, under the current care of an allergy/immunology specialist, requires non-beta-lactam antibiotics for an infection or colonisation with an organism-resistant to beta-lactam (eg, MRSA, ESBL producing gram negatives), emergency or trauma surgery, contraindication for oral provocation: (a) receiving more than 10 mg of prednisolone or equivalent daily, (b) receiving antihistamine therapies or (c) history of drug-associated anaphylaxis or idiopathic urticaria/anaphylaxis.
Study type	Interventional
	Allocation: randomised intervention model. Partial blinding, participants aware of assignment and outcome of testing, treating clinicians will be blinded to assignment and outcome of testing.
	Primary purpose: safety and feasibility

ESBL, Extended Spectrum Beta Lactamase; MRSA, Methicillin Resistant Staphylococcus Aureus.

period (72 hours post-surgery); and (3) median length of stay and inpatient mortality.

Participant timeline

A timeline of participant involvement in the study is summarised in figure 3.

Sample size

The sample size calculation for this feasibility and safety study is based on the precision of the estimates for the feasibility outcomes.

Feasibility considerations

We will estimate the proportion of patients randomised in the intervention arm that receive the intervention as per protocol with sufficient precision. Recruiting 49 patients in the intervention arm of the study would provide the precision (half-width of the 95% CI) of 8% to estimate the underlying proportion of patients treated per protocol to be 85% as per the definition provided earlier in this protocol.

Safety considerations

We will estimate the proportion of patients experiencing AEs causally related to the study in the intervention arm
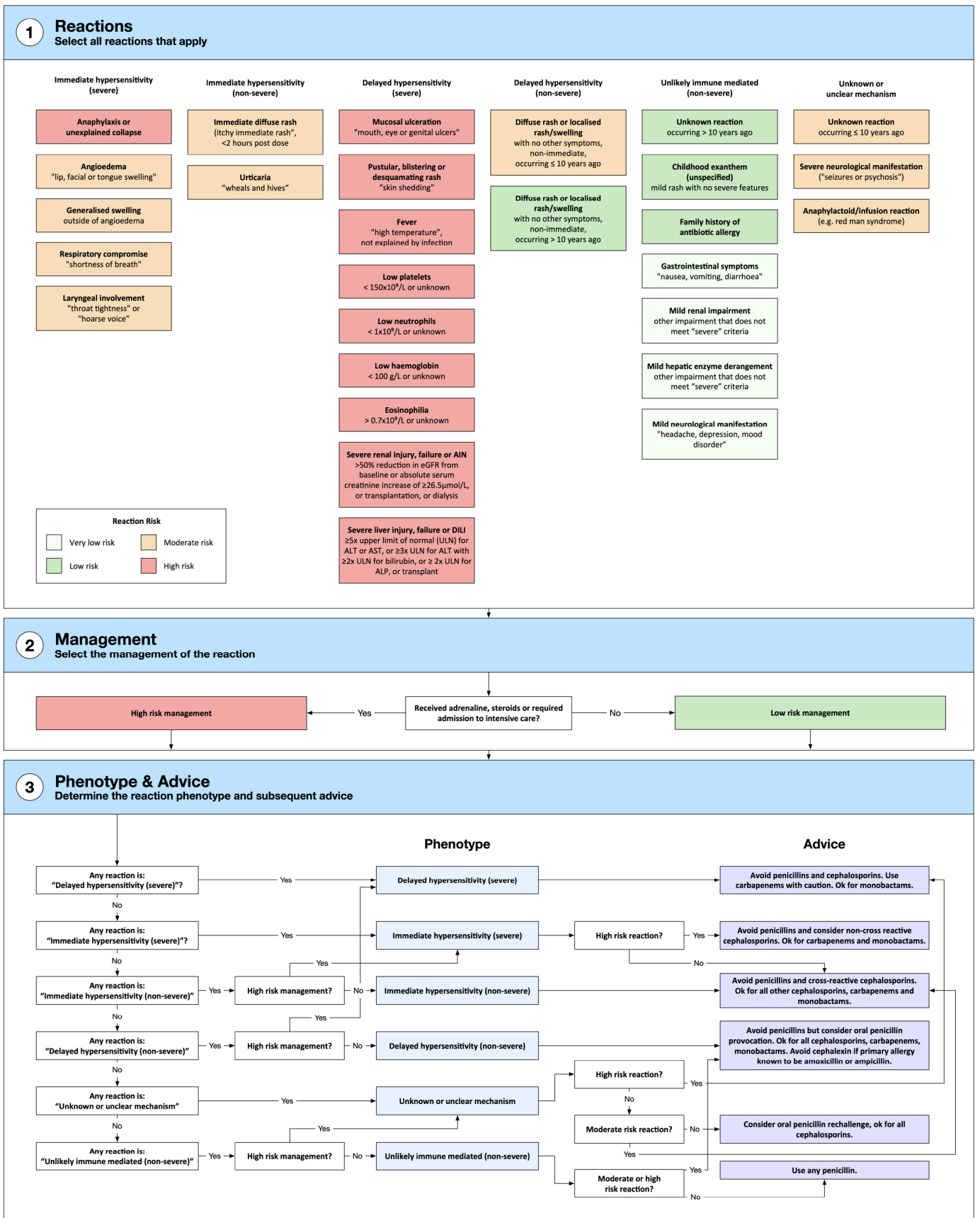
Figure 2 Risk stratification algorithm behind smartphone application. AIN, acute interstitial nephritis; ALT, alanine transaminase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate.

Table 2 Risk stratification recommendations by risk level

Risk	Colour on antibiotic allergy assessment Tool[8]	Recommendation
Low	White or green	► Recommendation for point-of-care oral penicillin provocation (if eligible) ► Point-of-care oral penicillin provocation can be performed on day of appointment or in intervening period between assessment and surgery if modifiable exclusion criteria initially met (eg, antihistamine utilisation) ► Recommendation for cefazolin perioperatively
Moderate	Orange	► Recommendation for NO point-of-care oral penicillin provocation ► Referral for routine clinical outpatient penicillin allergy testing ► If unable to attend outpatient allergy testing prior to surgery ► Recommendation for cefazolin perioperatively
High	Red	► Recommendation for NO point-of-care oral penicillin provocation ► Referral for routine clinical outpatient penicillin allergy testing ► If unable to attend allergy testing prior to surgery ► Recommendation for use of non-beta lactam for perioperative prophylaxis ► Utilise a ≥3rd generation cephalosporin or carbapenem (not for high risk delayed) for infective complications post-surgery (as per indication)

with sufficient precision. Recruiting 73 patients in the intervention arm of the study would provide the precision (half-width of the 95% CI) of 5% to estimate the underlying proportion of patients experiencing any

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Box 1 Outcome measures
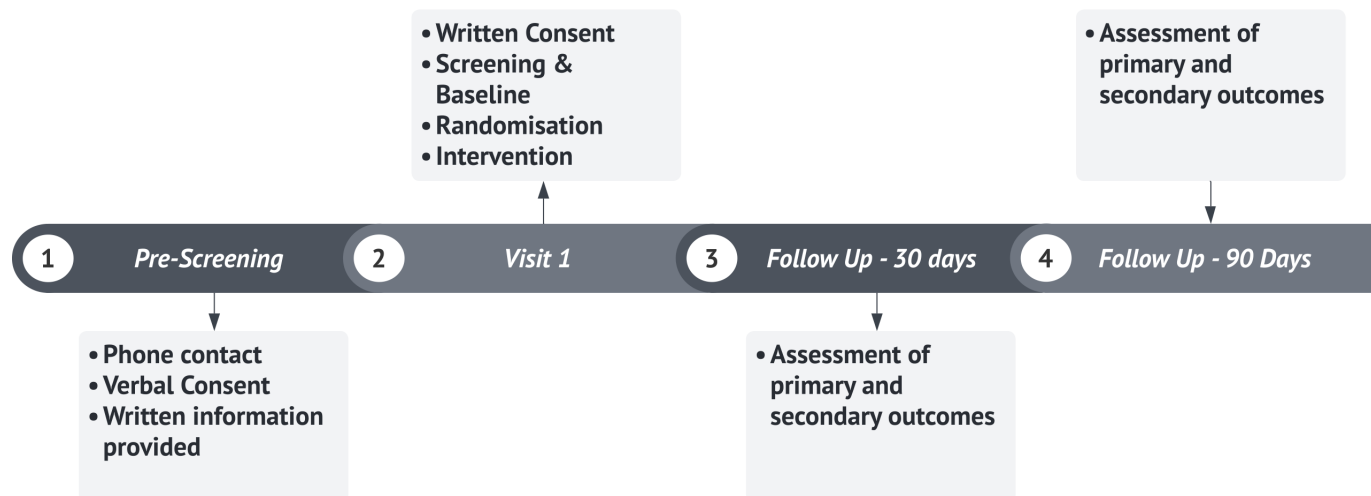
Primary outcomes

Feasibility outcome measures:
⇒ Feasibility of intervention delivery defined as the proportion of patients randomised to the intervention arm who had the intervention delivered as per protocol.
⇒ Feasibility of recruitment defined as the proportion of patients consenting to participation in the study as per protocol from eligible patients.

Safety outcome measures:
⇒ The proportion of patients with a penicillin allergy who experience an antibiotic associated AE and/or severe adverse drug reaction as per protocol definitions.

Secondary outcomes:
⇒ Proportion of patients with a penicillin allergy where a guideline preferred beta-lactam antibiotic is used for antibiotic prophylaxis.
⇒ Proportion of patients with a penicillin allergy that receive any beta-lactam in surgical prophylaxis.
⇒ Proportion of patients with a penicillin allergy that receive any beta-lactam in perioperative period (72 hours post surgery).
⇒ Proportion of patients with a penicillin allergy that develop a surgical site infection up to 90 days post-surgery.
⇒ Proportion of patients with a penicillin allergy that develop an acute kidney injury in the 72 hours post-surgery.
⇒ Proportion of patients with a penicillin allergy that utilise an appropriate antibiotic for surgical prophylaxis (defined by National Antimicrobial Prescribing Survey definitions).[27]
⇒ Time from antibiotic administration to surgical incision (mins).
⇒ Surgical operating time (mins).
⇒ Proportion of patients with a penicillin allergy with a non-elective admission to the intensive care unit unit in the 72 hours post-surgery.
⇒ Length-of-stay.
⇒ Inpatient mortality.

AE to the study to be 5%. The definition of serious AE includes any one of the following causally related to study intervention; death, life-threatening event, requires inpatient hospitalisation or causes prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, an event that requires intervention to prevent permanent impairment or damage. An antibiotic-associated AE is defined as any immune mediated (immediate (IgE) mediated or non-immediate (T-cell)) or side effect reactions (Type A) as judged by two independent reviewers.

Assuming 1:1 randomisation between two study arms, we would randomise 150 patients (sample size calculation to assessed safety requires 73 in each arm (146 total), total randomised rounded to 150 total) in total, providing sufficient precision for both feasibility and safety outcomes. Minimal loss to follow-up is expected as the primary outcomes are being assessed at the same visit as recruitment. This sample size is feasible, as we assume that 9% of all screened patients will report a penicillin allergy as per national data,[27] thus requiring us to screen up to 1750 patients. This will be achieved by four centres each contributing approximately 40 patients out of their general 480 patient per year cohort.

Recruitment

Patients planned for elective surgery and reviewed in perioperative clinic will be screened for eligibility by the clinical trial team prior. Those meeting eligibility criteria will be provided with 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. For 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.

Figure 3 Participant timeline.

METHODS: ASSIGNMENT OF INTERVENTIONS

Following informed consent, randomisation will be performed at an individual patient level. Participants will be randomly assigned in a ratio of 1:1 to either standard of care arm or the intervention arm. Randomisation will be performed via REDCap, a password-protected, secure website hosted on the Austin Health server, using a permuted block design, stratified by site. The treating clinicians (surgeons or perioperative anaesthetists) will carry out the enhanced allergy assessment but have no further role in treatment allocation or oral provocation.

Participants will not be blinded but perioperative physicians assessing participants will be blinded to the final intervention (patients will be assessed by study investigators in a separate location to perioperative assessing physicians). In regard to blinding of the perioperative physician and other treating clinicians, the result of the Antibiotic Allergy Assessment Tool and randomisation (control vs intervention arm) will not be made available. A recommendation for antibiotic utilisation following assessment and change in the beta-lactam allergy status (if applicable) of the medical record will be performed as part of routine clinical practice by study investigations prior to surgery. Consent is required for randomisation to the allergy assessment and potential oral beta-lactam provocation or outpatient allergy assessment

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

All data will be deidentified prior to any analyses and data sharing. Access to the original data will be restricted to study site(s) listed investigators and operators of PREPARE. Furthermore, all personnel have been instructed about the proper notation of collected documentation. Patient research data will only be accessed by the named investigators of PREPARE. Electronic records will be retained on password-protected computer(s) in databases requiring password access. This data will be stored separately from the master list of patient names. Any hard copies of data will be kept in locked facilities of the participating sites. Only study investigators will have access to the data. Patient data will be only be transferred and analysed in a coded form. Individual patients will not be identifiable from the presented or published material. Patient and research data will be stored on hard disk for a period of at least 7 years. After 7 years these files may be destroyed by erasure and/or incineration (for CD-ROM) unless decided by the principal investigator.

Statistical methods

Feasibility of intervention delivery and feasibility of recruitment will be reported as proportions with respective 95% CIs. The proportions of patients with a beta-lactam allergy who experience an antibiotic-associated AE and/or severe adverse drug reaction as per protocol definitions will be reported by group with respective 95% CIs and compared using modified Poisson regression model with robust SE estimation. Corresponding effect size will be reported as risk ratio with respective 95% CI.

Secondary outcomes will be reported by group and compared using logistic regression models. Details of statistical analysis will be documented in a separate Statistical Analysis Plan that will be developed and finalised prior to the study database lock.

METHODS: MONITORING

Structured oversight of the trial will be provided via a multidisciplinary trial committee made up of individuals not directly involved in recruitment of participants. The committee will be responsible for reviewing individual safety reports and aggregate event rates, as well as maintaining oversight of protocol adherence. Regular reviews will be conducted every 10–20 participants recruited.

ETHICS AND DISSEMINATION

Ethical approval was obtained on 4 April 2018 by the Austin Health Human Research Ethics Committee

(reference: HREC/17/Austin/575), with an anticipated completion date of 31 March 2022.

The results of this study will be published in peer-reviewed journals, as well as presented at national and international conferences. Pertinent results will be shared with participating institutions prior to publication.

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REFERENCES
1 Trubiano JA, Chen C, Cheng AC, *et al*. Antimicrobial allergy " labels " drive inappropriate antimicrobial prescribing: lessons for stewardship. *J Antimicrob Chemother* 2016;71:1715–22.
2 Trubiano JA, Cairns KA, Evans JA, *et al*. The prevalence and impact of antimicrobial allergies and adverse drug reactions at an Australian tertiary centre. *BMC Infect Dis* 2015;15:572.
3 Trubiano JA, Beekmann SE, Worth LJ, *et al*. Improving antimicrobial stewardship by antibiotic allergy delabeling: evaluation of knowledge, attitude, and practices throughout the emerging infections network. *Open Forum Infect Dis* 2016;3:ofw153.
4 Trubiano JA, Worth LJ, Urbancic K, *et al*. Return to sender: the need to re-address patient antibiotic allergy labels in Australia and New Zealand. *Intern Med J* 2016;46:1311–7.
5 Trubiano J, Phillips E. Antimicrobial stewardship's new weapon? A review of antibiotic allergy and pathways to " de-labeling. " *Curr Opin Infect Dis* 2013;26:526–37.
6 Devchand M, Kirkpatrick CMJ, Stevenson W, *et al*. Evaluation of a pharmacist-led penicillin allergy de-labeling ward round: a novel antimicrobial stewardship intervention. *J Antimicrob Chemother* 2019;74:1725–30.
7 Chua KYL, Vogrin S, Bury S, *et al*. The penicillin allergy delabeling program: a multicenter whole-of-hospital health services intervention and comparative effectiveness study. *Clin Infect Dis* 2021;73:487–96.
8 Devchand M, Urbancic KF, Khumra S, *et al*. Pathways to improved antibiotic allergy and antimicrobial stewardship practice: the validation of a beta-lactam antibiotic allergy assessment tool. *J Allergy Clin Immunol Pract* 2019;7:1063–5.
9 Barlam TF, Cosgrove SE, Abbo LM, *et al*. Implementing an antibiotic stewardship program: guidelines by the infectious diseases Society of America and the Society for healthcare epidemiology of America. *Clin Infect Dis* 2016;62:e51–77.
10 Australian Commission on Safety and Quality in Health Care. Antimicrobial stewardship in australian health care. 2018. Available: https://www.safetyandquality.gov.au/our-work/antimicrobial-stewardship/antimicrobial-stewardship-australian-health-care-ams-book
11 Trubiano JA, Pai Mangalore R, Baey Y-W, *et al*. Old but not forgotten: antibiotic allergies in general medicine (the AGM study). *Med J Aust* 2016;204:273.
12 Jeffres MN, Narayanan PP, Shuster JE, *et al*. Consequences of avoiding β-lactams in patients with β-lactam allergies. *J Allergy Clin Immunol* 2016;137:1148–53.
13 Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;133:790–6.
14 Blumenthal KG, Lu N, Zhang Y, *et al*. Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study [BMJ (Clinical research ed) 2018;361:k2400]. *BMJ* 2018;361:k2400.
15 Blumenthal KG, Ryan EE, Li Y, *et al*. The impact of a reported penicillin allergy on surgical site infection risk. *Clin Infect Dis* 2018;66:329–36.
16 Charneski L, Deshpande G, Smith SW. Impact of an antimicrobial allergy label in the medical record on clinical outcomes in hospitalized patients. *Pharmacotherapy* 2011;31:742–7.
17 Trubiano JA, Thursky KA, Stewardson AJ, *et al*. Impact of an integrated antibiotic allergy testing program on antimicrobial stewardship: a multicenter evaluation. *Clin Infect Dis* 2017;65:166–74.
18 Trubiano JA, Smibert O, Douglas A, *et al*. The safety and efficacy of an oral penicillin challenge program in cancer patients: a multicenter pilot study. *Open Forum Infect Dis* 2018;5:ofy306.
19 McDanel DL, Azar AE, Dowden AM, *et al*. Screening for beta-lactam allergy in joint arthroplasty patients to improve surgical prophylaxis practice. *J Arthroplasty* 2017;32:S101–8.
20 Vaisman A, McCready J, Hicks S, *et al*. Optimizing preoperative prophylaxis in patients with reported β-lactam allergy: a novel extension of antimicrobial stewardship. *J Antimicrob Chemother* 2017;72:2657–60.
21 Blumenthal KG, Shenoy ES, Hurwitz S, *et al*. Effect of a drug allergy educational program and antibiotic prescribing guideline on inpatient clinical providers' antibiotic prescribing knowledge. *J Allergy Clin Immunol Pract* 2014;2:407–13.
22 Blumenthal KG, Shenoy ES, Varughese CA, *et al*. Impact of a clinical guideline for prescribing antibiotics to inpatients reporting penicillin or cephalosporin allergy. *Ann Allergy Asthma Immunol* 2015;115:294–300.
23 Shenoy ES, Macy E, Rowe T, *et al*. Evaluation and management of penicillin allergy: a review. *JAMA* 2019;321:188–99.
24 Chan A-W, Tetzlaff JM, Gøtzsche PC, *et al*. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
25 Craig P, Dieppe P, Macintyre S, *et al*. Developing and evaluating complex interventions: the new medical Research Council guidance. *BMJ* 2008;337:a1655.
26 Carroll C, Patterson M, Wood S, *et al*. A conceptual framework for implementation fidelity. *Implement Sci* 2007;2:40.
27 Australian Commission on Safety and Quality in Health Care. Antimicrobial prescribing practice in australian hospitals: results of the 2019 hospital national antimicrobial prescribing survey. 2021. Available: https://irp-cdn.multiscreensite.com/d820f98f/files/uploaded/Hospital%20NAPS%20Report_2019.pdf [Accessed 15 Mar 2021].