PROTOCOL

PROlonged versus **S**ingle dose in **PE**nicillin oral **C**hallenge **T**esting parallel randomized feasibility placebo c**O**ntrolled t**R**ial - **PROSPECTOR Study**

Protocol Number:
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Sponsor/s:
Austin Health

Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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STUDY SYNOPSIS

Title:	Prolonged versus single dose in penicillin oral challenge testing parallel randomized feasibility placebo controlled trial
Short Title:	PROSPECTOR
Design:	Multi-center parallel double-blinded placebo-controlled feasibility randomized clinical trial
Study Centers:	Austin Health – Victoria, Australia Peter MacCallum Cancer Center – Victoria, Australia St George Hospital – NSW, Australia Royal Brisbane and Womens Hospital – QLD, Australia McGill University Health Centre (MUHC) - Canada Groote Schuur Hospital – South Africa Herlev and Gentofte Hospital – Denmark
Study Question:	Is a placebo controlled trial feasible for evaluating whether prolonged oral challenge is required in patients undergoing allergy/immunology evaluation for penicillin allergy?
Intervention	Prolonged oral penicillin challenge
Control	Single dose oral challenge
Study Objectives:	Evaluate the feasibility of a placebo-controlled trial and inform the design of a definitive trial evaluating whether prolonged oral challenge (5-day) is superior to standard care (single dose oral challenge) in patients reporting a penicillin allergy to ascertain a confirmed immune-mediated adverse reaction.
Primary outcomes	**Compliance to the intervention, need for unblinding and recruitment feasibility.**
Secondary outcomes	**Feasibility outcome measures**: • Recruitment rate per site • Randomisation to recruitment ratio • Withdrawal • Loss to follow-up • Missing data • Adherence to the protocol **Safety outcome measures:** • Severe adverse reaction – anaphylaxis or death • Immune-mediated adverse event OR severe adverse drug reaction as per protocol definitions • Non-immune mediated adverse event **Exploratory efficacy outcomes** • Positive oral challenge (immune mediated reaction) within 7 days post first dose • *C. difficile* infection at 30 day and 90-day follow up • Multidrug resistant infection at 30 day and 90-day follow up as per protocol definitions

	• Cost effectiveness analysis of placebo vs open label trial
Inclusion Criteria:	1. Adult patients referred to the inpatient or outpatient allergy services for a penicillin allergy history that describe a delayed immune-related allergy history or unknown reaction who tolerate first single-dose of an oral penicillin challenge (to the implicated penicillin). 2. Willing and able to give consent and undergo telehealth review
Exclusion Criteria:	1. Patient age is < 18 years; 2. Any other illness that, in the investigator's judgement, will substantially increase the risk associated with subject's participation in this study; 3. Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis to beta-lactam 4. Inpatients concurrently receiving beta-lactam antibiotic therapy
Number of Planned Subjects:	120 (60 per arm)
Investigational product:	Not applicable
Safety considerations:	Serious adverse event as per definition Antibiotic associated immune mediated adverse event as per definition An independent data safety management board (DSMB) will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety.
Statistical Methods:	Projected sample size: 120 participants will enable feasibility outcomes with <20% absolute confidence interval width. Outcome will be presented as number and proportion of participants with 95% confidence interval. Efficacy outcomes will also be presented as relative risk and relative difference with 95% confidence intervals.
Subgroups:	Setting – inpatient vs outpatient Risk - PEN-FAST < 3 vs ≥ 3 Severity – RegiSCAR < 2 vs ≥ 2

1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
ST	Skin testing to assess for drug allergy
PT	Prick skin testing to assess for drug allergy
IDT	Intra-dermal skin testing to assess for drug allergy
Oral provocation (challenge)	The provision of a test dose of drug to prove or disprove allergy
Oral penicillin provocation (challenge) – Single Dose	In brief, following informed consent, a dose of penicillin (orally) is given to patients with a 1-hour observation period post dose. Vital signs are monitored at baseline and as needed. Emergency medication is available on site (including adrenaline administration).
Oral penicillin provocation (challenge) – Prolonged (5-day)	In brief, following informed consent, a dose of penicillin (orally) is given to patients with a 1-hour observation period post dose initial dose and then twice daily internal for 5 days. Vital signs are monitored at baseline and as needed. Emergency medication is available on site (including adrenaline administration) for initial dose
Negative oral penicillin provocation (challenge)	No antibiotic associated immune mediated reactions at 48 hours post last dose of oral penicillin challenge
Positive immune mediated oral penicillin provocation (challenge)	A patient-reported immune-mediated adverse event within 48 hours following the last test dose and confirmed by two independent specialist reviews blinded to the intervention.
Serious adverse event	A serious adverse event will be defined as any adverse drug event/experience occurring at any dose that in the opinion of the investigators is causal for any of these outcomes: (1) death; (2) life threatening reaction; (3) inpatient hospitalization; (4) results in persistent or significant disability/incapacity; (5) congenital anomaly or birth defect; or (6) requires intervention to prevent permanent impairment or damage.
Antibiotic Associated Immune Mediated Adverse Event	Any immune mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of the last oral challenge dose, confirmed by two independent specialist reviews blinded to the intervention.
Antibiotic Associated non-immune Adverse Event	An antibiotic associated adverse event will include any non-immune mediated reaction (e.g. nausea, vomiting, diarrhea etc.) within 48 hours of completion of the last oral challenge dose, confirmed by two independent specialist reviews blinded to the intervention.
Cutaneous adverse reaction	Any objective new onset cutaneous rash noted at 7 day follow up post first dose, confirmed by two independent specialist reviews blinded to the intervention.

Penicillin allergy label	A patient reporting an allergy to any of: penicillin "unspecified", penicillin VK, penicillin G, amoxicillin, ampicillin, flucloxacillin, dicloxacillin.
Low risk penicillin allergy	Unknown > 10 years, maculopapular rash (MPE) greater than 10 years prior, Type A adverse drug reaction (ADR) as per published definition [1], local injection site reaction, childhood benign exanthema.
Delabelled	The removal of a patient's reported allergy if no immune-mediated adverse event is noted following direct oral provocation or challenge with implicated drug
NSP	Narrow spectrum penicillin including Penicillin VK, penicillin G, amoxicillin, ampicillin, flucloxacillin, dicloxacillin.
NSB	Narrow spectrum beta-lactam including the NSP + cefazolin, cefuroxime and cephalexin.
Restricted antimicrobial agents	Antimicrobial agents that include cefepime, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, meropenem, moxifloxacin, piperacillin/tazobactam, teicoplanin, tobramycin and vancomycin.
PEN-FAST	Penicillin allergy decision rule
RegiSCAR	A validated scoring system to identify drug reaction with eosinophilia and systemic symptoms
Multi-drug resistant infection	Infection cause by pathogen that is resistant to one drug from at least three antibiotic classes

2. STUDY SITES

a. STUDY LOCATION/S

Site	Address	Contact Person	Phone	Email
Austin Health	145 Studley Road, Heidelberg VIC 3084	A/Prof Jason Trubiano	(03) 94966709 0466067000	Jason.trubiano@austin.org.au
Peter MacCallum Cancer Center	305 Grattan Street, Melbourne, VIC 3000	Dr Morgan Rose	(03) 94966709 0466067000	Morgan.rose@petermac.org
St George Hospital		Dr Richard Sullivan		Richard.sullivan@health.nsw.gov.au
	1650 Cedar Ave, Montreal,	Dr Ana Copaescu		

Montreal General Hospital (MGH) McGill University Health Centre (MUHC) - Glen site	Quebec H3G 1A4, Canada 1001 boul. Decarie Montreal, Quebec, H4A 3J1, Canada			ana.copaescu@unimelb.edu.au
Herlev and Gentofte Hospital	Borgmester Ib Juuls Vej 11, 2730 Herlev, Denmark	A/Prof Lene Garvey	+45 38 68 38 68	lene.heise.garvey@regionh.dk
Groot Schuur Hospital	Main Rd, Observatory, Cape Town, 7935, South Africa	A/Prof Jonny Peter	+27 21 404 9111	jonny.peter@uct.ac.za

3. INTRODUCTION/BACKGROUND INFORMATION

b. LAY SUMMARY

Penicillin allergies are a major burden on patients and health care worldwide. Currently, up to 1 in 4 hospitalised patients admitted to hospital will report an antibiotic allergy, many of which limit appropriate antibiotic use and lead to poorer health outcomes. In some instances, patients will be given a single or multiple test doses to determine if a patient is truly allergic. This study will further research to determine if a single dose or multiple dose challenge (5-days) is able to elicit true penicillin allergy and examine the unintended consequences associated with each type of challenge.

c. INTRODUCTION

Penicillin allergies are highly prevalent in the healthcare setting and associated with second-line inferior antibiotics being prescribed. An incorrect penicillin allergy label leads to increased risk of resistant organisms, side effects from second-line antibiotics as well as increased medical costs [2]. The gold standard for penicillin allergy testing is an oral challenge – either direct or following skin testing. What remains unknown is if a single dose is sufficient to

determine if the patient has an immune mediated penicillin allergy or if a prolonged oral challenge (≥ 3 days) is required.

This study aims to assess the feasibility of a placebo-controlled trial to compare single dose oral challenge versus prolonged oral challenge (5-day twice daily dosing) for identifying immune-mediated penicillin allergy.

d. BACKGROUND INFORMATION

Patient-reported penicillin allergies result in poor health outcomes for patients and drive inappropriate antibiotic prescribing, antimicrobial resistance and healthcare costs [3-7]. Our previous work has shown that more than 85% of penicillin allergies can be removed by formal skin prick allergy testing [8], and 96-98% with low-risk allergies can be removed by point-of-care oral challenge [9]. From an Australian perspective we identified that the rates of delayed reactions after single dose challenge were low (3 immune positive challenges from 200 undertaken occurring between days 5 and 7 post testing), however in this a larger proportion of patients received ongoing inpatient therapy following the initial negative single dose oral challenge [10]. In a randomised control trial (PALACE study) including patients with delayed phenotypes, single dose oral penicillin challenge was still able to elicit delayed-onset allergy in 12 of 377 enrolled patients (Copaescu *et al.* Unpublished 2023). On further examination of the PALACE study data the rate of 5-day presumed immune mediated adverse event was 3.2%.

The current Drug Allergy Practice Parameters recommend “against the routine use of multiple-day challenges in the evaluation of penicillin allergy”, providing a “strong recommendation” but with “low certainty of evidence”[11]. In Europe, a mixture of observational and retrospective studies has suggested that extended challenges ranging from 3 to 10 days may be superior to single dose challenges at excluding delayed immune reactions, however the reported prevalence of delayed reactions is highly variable (5-12% of patients) and many were reliant on patient self-reporting [12-18]. This is converse to the North American experience where delayed prolonged challenges have been associated with low rates of delayed reactions (0-1.8%)[19-22]. Whilst a study of children demonstrated that delayed reactions may occur <7 days following a single challenge[23]. **Therefore, whilst oral challenge is the well-defined gold standard for penicillin allergo-immunological investigation, limited controlled evidence is available regarding the safety and efficacy of single dose versus prolonged oral challenge.**

Blinded randomized placebo-controlled trials have not been previously used in any drug allergy trials. **The aim of this study is to assess whether blinded randomised placebo-controlled trials are feasible, and to inform the design and sample size calculations for a definitive trial.**

4. STUDY OBJECTIVES

e. HYPOTHESIS

Placebo controlled trial is a feasible study design with high compliance to the intervention, recruitment and small need for unblinding.

f. STUDY AIMS

Evaluate the feasibility of placebo-controlled trial comparing prolonged oral challenge (5-day) versus single dose challenge for evaluation of immune-mediated penicillin allergy in the inpatient and outpatient setting to inform the design of a definitive trial.

g. OUTCOME MEASURES

Primary outcomes:

- Compliance with the intervention (number and percentage of participants taking at least 80% of the doses)
- Need for unblinding (number and percentage of participants being intentionally or unintentionally unblinded)
- Recruitment to eligibility ratio (percentage of participants consenting to participate in the study as per protocol from eligible patients)

Secondary outcomes:

Feasibility outcomes:

- Recruitment rate per site (number of participants recruited / month)
- Randomisation to recruitment ratio (percentage of participants randomised to the intervention arm from recruited patient)
- Withdrawal (number and percentage of participants that withdrew from the study)
- Loss to follow-up (number and percentage of participants who were lost to follow-up at each time point)
- Missing data (number and percentage of participants with missing data for each efficacy outcome)
- Protocol compliance (number and percentage of participants per each type of protocol violation)

Safety outcome measures:

- Severe adverse reaction – anaphylaxis/death (number and percentage of participants)
- Immune-mediated adverse event OR severe adverse drug reaction as per protocol definitions (number and percentage of participants, stratified by antibiotic associated vs non-antibiotic associated)
- Non-immune mediated adverse event (number and percentage of participants, stratified by antibiotic associated vs non-antibiotic associated)
- Any cutaneous adverse reaction (number and percentage of pariticipants)

Exploratory efficacy outcomes

- Positive oral challenge (i.e. immune mediated reaction up to and including day 7 following the first test dose, number and percentage of participants)
- *C. difficile* infection at 30-day and 90-day follow up (number and percentage of participants)
- Isolation of a multidrug resistant infection at 30-day and 90-day follow up as per protocol definitions (number and percentage of participants)

Cost effectiveness analysis

- Cost effectiveness of placebo vs open label trial

5. STUDY DESIGN

h. STUDY TYPE & DESIGN & SCHEDULE

This is an international multi-center, prospective blinded feasibility trial (Summary in **Figure 1**) to be conducted at Austin Health (Victoria, Australia), Peter MacCallum Cancer Centre (Victoria, Australia), St George Hospital (NSW, Victoria), McGill University Health Centre – Glen site (MUHC, Canada), Montreal General Hospital (MGH, Canada), Herlev and Gentofte Hospital (Demark), Groot Schuur Hospital (South Africa) .

Eligible patients referred to the outpatient clinic or inpatient service reporting a penicillin allergy will be identified and assessed with a standard clinical history (including use of digital adapted Antibiotic Allergy Assessment Tool[24]) and subsequent calculation of the PEN-FAST score (**Figure 2**) and RegiSCAR score. PEN-FAST is a three-point clinical assessment tool recently externally validated in a multicenter study, with a PEN-FAST score of < 3 associated with

96.7% negative predictive value [25]. RegiSCAR is a validated scoring system to define drug reaction with eosinophilia and systemic symptoms[26].

All patients will undergo routine management as per the treating clinicians which may include skin prick and intradermal beta-lactam testing (if required, Appendix 1), followed by oral penicillin challenge (i.e. amoxicillin) in the setting of negative skin testing (if performed). Patients may also proceed directly to direct oral penicillin challenge depending on trial setting practices.

The participant will receive a single dose amoxicillin challenge in clinic/on the ward following baseline vital signs as per the site current standard of care (Day 0). The patient must report a reaction to amoxicillin or penicillin unspecified, and they will be administered amoxicillin. The amoxicillin should also be administered as a single available dose (250-500mg as per site practice) and patient observed for 1-2 hours as per site local practice. If at any stage antibiotic associated adverse event is noted, standard of care treatment is offered by the attending clinician (e.g.. adrenaline for immediate hypersensitivity reaction). If the patient passes the oral challenge without reported immune-mediated adverse events, they are then eligible for recruitment and randomisation into the study.

Following informed written consent, we will randomise 120 patients (1:1 ratio) into the intervention group (5-day oral challenge) or control group (single dose challenge followed by 5-day placebo).

Patients on discharge irrespective of control or intervention arm, will be supplied with a prescription for oral corticosteroids and antihistamines to be used in the setting of an immune-mediated positive oral challenge, as instructed by the site investigators at time of the day 1,5 and 14 reviews. Participants will be instructed by site investigators to fill this script at their own expense if required.

Intervention:

If recruited to the ***intervention arm***, the participant will then receive a 5-day course of oral amoxicillin 500mg twice daily (BD) frequency, commencing the day following the hospital administered single dose (Day 1).

Control:

If recruited to the ***control arm***, the participant will receive no further therapeutic doses, but will receive oral placebo twice daily (BD) for 5 days.

All clinicians and participants will be blinded to the treatment allocation, pharmacy dispensing team will remain unblinded. A telehealth review will be performed on days 1, 5 and 14 by trial site specialist allergy healthcare provider. If patients are inpatients at the time, then this review will be performed at the patient bedside. At each telehealth review compliance will be recorded by reporting the number of doses taken and participants will be asked about any other concurrent antibiotic therapy. If a positive oral challenge is reported, a summary of the patient reported symptoms utilising a standardised questionnaire and clinical photography of any rash, cutaneous or mucosal changes will be sent to an independent review panel consisting of an allergist and dermatologist blinded to the intervention to ascertain if the reported reaction is an "immune mediated adverse drug reaction". This panel will be a central panel for the whole study and blinded to the study arms.

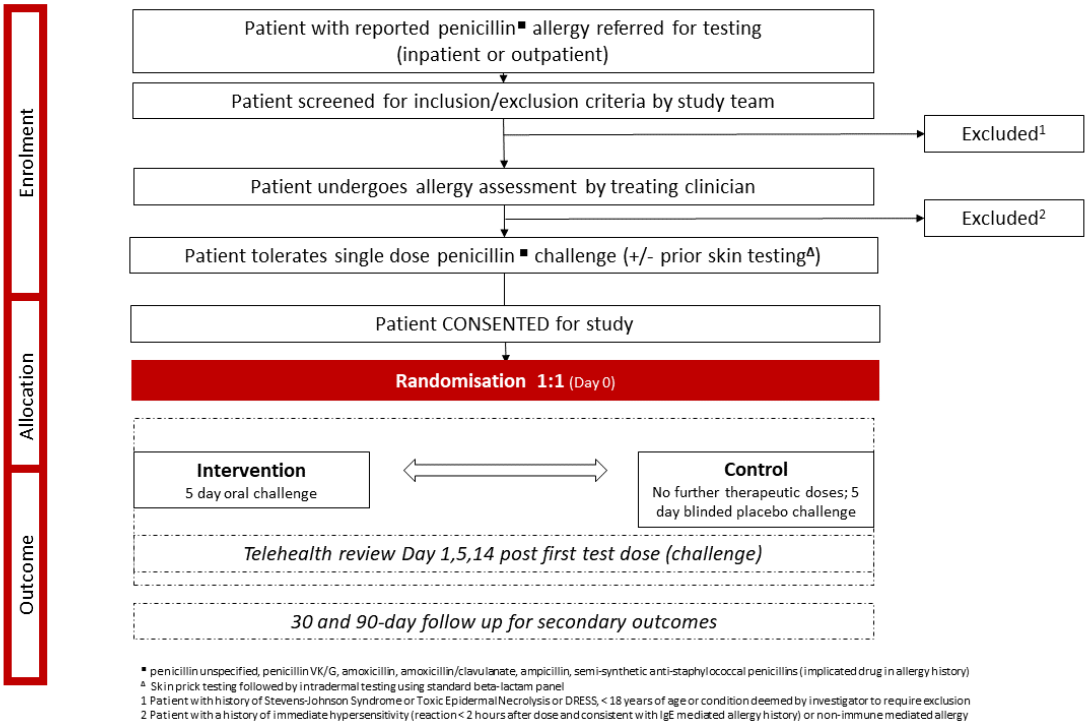
There will be no additional blood sampling or testing for patients in either arm of the trial. Patients in both groups will be able to directly contact a member of the clinical team (telehealth) if any serious or antibiotic associated adverse events occurs in the between the designated follow up times of Day 1, 5 and 14.

Follow-up: A 30-day and 90-day post-randomisation telephone questionnaire and assessment of the medical record at each hospital site will be undertaken (Appendix 2). The follow up is to assess for secondary outcomes including – antibiotic-associated diarrhoea; *Clostridioides difficile* infection or acquisition of a multi-drug resistant organism. Patients at 90-day follow up will be unblinded and offered a prolonged oral challenge, if preferred by site investigators, if they were negative on oral challenge and recruited to the placebo arm.

Blinding: 1. placebo and active are visually identical, prepared by Central Pharmacy Logistics experienced in compounding and blinding trial medications
2. placebo contains Microcrystalline cellulose MCC; an inert substance that is also gluten free
3. active contains Amoxicillin 500mg
4. dose schedule: both arms will receive 5 day course of BD capsules.

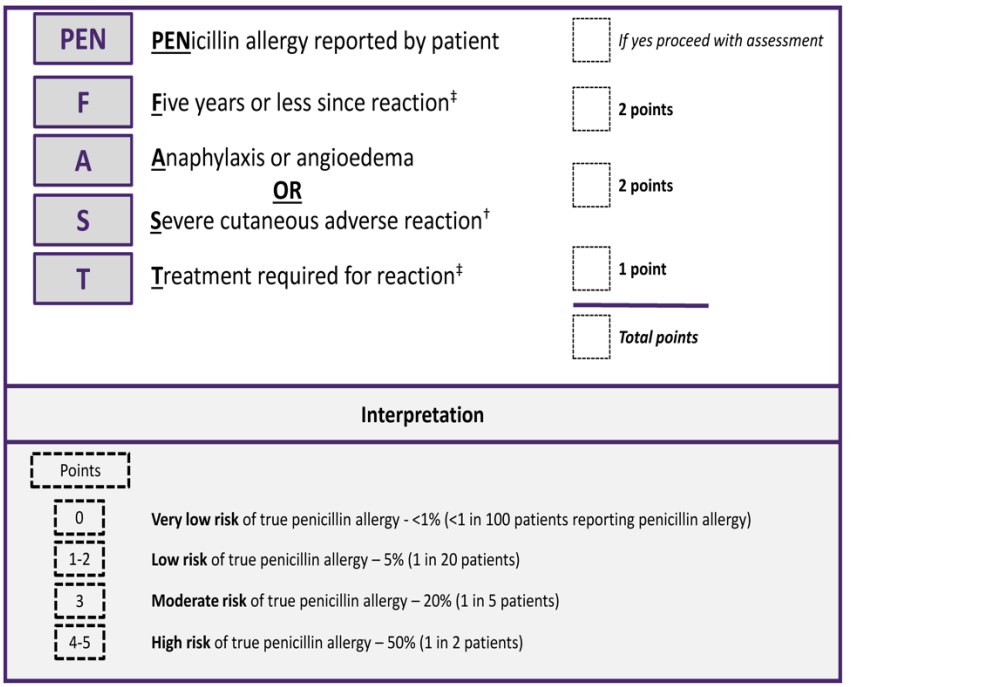
Unblinding: Patients can unblinded, in addition to the designated 90-day follow up period, if during the 14 day follow up period a serious adverse event (SAE) is recorded as per study definitions and the principle investigator deems this appropriate.

FIGURE 1 – OVERVIEW OF THE STUDY DESIGN



▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, semi-synthetic anti-staphylococcal penicillins (implicated drug in allergy history)
Δ Skin prick testing followed by intradermal testing using standard beta-lactam panel
1 Patient with history of Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis or DRESS, < 18 years of age or condition deemed by investigator to require exclusion
2 Patient with a history of immediate hypersensitivity (reaction < 2 hours after dose and consistent with IgE mediated allergy history) or non-immune mediated allergy

FIGURE 2 – PEN-FAST CLINICAL DECISION RULE



† Severe cutaneous adverse drug reaction – Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP)
‡ Or Unknown

i. STANDARD CARE AND ADDITIONAL TO STANDARD CARE PROCEDURES

Standard Care Procedures		
Procedures	**Time/Visit**	**Dosage/Volume**
Skin testing	30 min	n/a
Single dose oral challenge	60-120 min	250-500mg BD
Prolonged oral challenge	5 days (BD dosing)	500mg BD

j. RANDOMIZATION

Permuted block design randomisation will be used, stratified by the hospital site and setting (inpatient vs outpatient). While block design might result in larger treatment imbalances, such

design is preferred to overcome logistical difficulties. Randomization will be performed by the pharmacy dispensing team via *REDCap* just prior to the intervention. The allocation sequence will be concealed until the time of the randomisation. Participants and clinicians will be blinded to the treatment allocation. Pharmacy dispensing team will remain unblinded. Central independent review panel ascertaining the reactions will be also blinded to the treatment allocation.

k. STUDY METHODOLOGY

All eligible patients who have a history of penicillin allergy will be evaluated and those meeting inclusion/exclusion criteria will receive a single dose oral challenge. Those tolerating first dose will be randomized to either:

No further therapeutic doses post initial single dose, but provided blinded 5-day placebo oral challenge (control)

OR

Prolonged 5-day oral amoxicillin challenge (intervention)

6. STUDY POPULATION

l. RECRUITMENT PROCEDURE

All adult patients referred to the outpatient clinic or inpatient service that have a documented or reported penicillin allergy will be screened for eligibility.

m. INCLUSION CRITERIA

1. Adult patients referred to the outpatient allergy clinic or inpatient allergy service for a penicillin allergy history (i.e. amoxicillin or penicillin unspecified)
2. Adult patients with an immune-mediated penicillin allergy history
    1. Delayed phenotype (> 2 hours post dose)
    2. Or unknown timing
3. Tolerated first dose of an oral penicillin challenge
4. Being challenged to amoxicillin
5. Willing and able to give consent
6. Willing and able to undergo telehealth or in clinic review post challenge

n. EXCLUSION CRITERIA

Patients will be **EXCLUDED** from the study if any ONE of the following criteria is present:

1. Patient age is < 18 years;
2. Any other illness that, in the investigator's judgement, will substantially increase the risk associated with subject's participation in this study
3. Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis to beta-lactam
4. 4. Inpatients receiving concurrent beta-lactam antibiotic therapy

o. CONSENT

All eligible patients will be provided with a verbal explanation of the project. They will also be provided with a paper or electronic consent form (depending on the local practices). If required, a copy will be given to the patients to further discuss with their treating medical team or family. A thorough assessment of the participant's competence and capacity to make a valid informed decision will be made by one of the study investigators prior to the patient being recruited. All patients will be deemed competent if they:

1. Are able to comprehend and retain information relevant to making the decision;
2. Understand the information and implications of the decision;
3. Are able to weigh the information in the balance and arrive at a decision.

7. PARTICIPANT SAFETY AND WITHDRAWAL

p. RISK MANAGEMENT AND SAFETY

Several previous studies performed at Austin Health have assessed the safety of oral penicillin provocation utilizing validated risk assessment tools [9, 24, 25]. All previous studies have reported no serious adverse effects from such treatment. Several have reported potential benefit. Accordingly, we believe the study carries a high level of safety.

The types of side effects include allergic reactions such as mild rash (i.e. 2 in 100) or anaphylaxis (i.e.1 in 10,000) or severe cutaneous adverse reaction (i.e. extremely rare event without available data).

Because of this risk, the initial dose challenge is done in an outpatient or inpatient hospital setting with surveillance from the medical staff (doctors and nurses). All the outpatient clinics are equipped with anaphylaxis management kits and have access to resuscitation equipment as needed. Patients are supervised in the clinic for minimum one hour after the challenge and with regular telehealth review up to 14 days post initial dose challenge.

An independent data safety management board (DSMB) will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if an increased recruitment effort is required. The DSMB will make recommendations as to

whether the study should continue or be terminated, consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant enrolment).

q. Handling of Withdrawals

Participants may withdraw from the study at any point. In these circumstances, the participant's data collected before the withdrawal might be included in the analysis.

r. Replacements

No withdrawals post randomization will be replaced.

8. Statistical Methods

s. Sample Size Estimation & Justification

Sample size of 120 participants (60/group) was chosen as this would give a precise estimate of feasibility outcomes with width of confidence interval being < 20% for any proportion. Such a sample size would also likely provide a reliable estimate of effectiveness as it has been shown that with binary outcome gain in precision is smaller once each group reaches 60 participants [27]. This sample size also likely represents >9% of the definitive trial's sample size (to detect 5% difference assuming 8% event rate with 90% power and 5% significance level, a total of almost 900 participants would be required)[27].

t. Statistical Methods To Be Undertaken

Results will be presented according to CONSORT guidelines for feasibility studies [28].

Patient characteristics and penicillin allergy history will be presented by arm using median (interquartile range) for continuous variables and count (percentage) for categorical variables.

Binary outcomes will be presented as count and percentage with 95% exact confidence intervals. All outcomes (where feasible) will be presented as overall, by study arm and by setting. Exploratory efficacy outcomes will also be presented as absolute (risk difference) and relative difference (risk ratio) with 95% confidence intervals. No statistical tests will be performed. Amount and pattern of missing data will be explored.

9. STORAGE OF BLOOD AND TISSUE SAMPLES

u. DETAILS OF WHERE SAMPLES WILL BE STORED, AND THE TYPE OF CONSENT FOR FUTURE USE OF SAMPLES

Not applicable.

10. DATA SECURITY & HANDLING

v. DETAILS OF WHERE RECORDS WILL BE KEPT & HOW LONG WILL THEY BE STORED

Patient clinical details and demographics will be recorded on data collection forms usually used in the outpatient clinic at each participating center. Completed forms will be kept in the Department of Infectious Diseases at the Austin Hospital, Peter MacCallum Cancer Center, and the Allergy-Immunology departments at the MUHC, Groote Schuur Hospital and Herlev and Gentofte Hospital

The collected data from every institution will then be stored on an electronic database (i.e. REDCap University of Melbourne) on password-protected computers. The data stored in the central REDCap database will be de-identified. Paper data and study related documents used in this study will be de-identified and only a master log will be maintained at the individual study site to be able to re-identify participants in the setting of a severe adverse event. The log will be locked in a protected office. All data for the study will be retained for a period of fifteen years after which all electronic and paper data will be destroyed in accordance with the hospital policy in place at the time. If the combination of these routinely collected data and information derived from this study provides useful clinical insights into the management of penicillin allergy, we plan to publish our findings. Authorship will be determined by the Investigational team with reference to the International Committee of Medical Journal Editors guidelines. Only aggregated non-identifiable patient data will be presented or published.

w. CONFIDENTIALITY AND SECURITY

An independent data safety management board (DSMB) will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety.

x. ANCILLARY DATA

Not applicable.

11. APPENDIX 1 – DRUG ALLERGY TESTING CONCENTRATIONS

If skin testing is performed a recommended panel is provided below which treating teams may wish to employ or use their own routine testing panel

A. Skin Prick Testing (Read at 15 minutes)

Time applied Time read

	Wheal	Flare	Positive	Negative	Signature
Histamine 10mg/ml					
Sodium Chloride 0.9%					
Diater PPL (major determinant)*					
Diater MDM (minor determinant) (if available)					
Ampicillin 20-25mg/ml OR amoxicillin 20-25mg/ml					
Penicillin 10 000 U/ml					

* Depending on site availability, major determinant Pre-Pen® can also be used

B. Intradermal Testing (0.02 ml) (Read at 15 minutes)

Time applied Time read

	Baseline reading	Final reading	Result	Signature
Sodium Chloride 0.9%				
Diater PPL (major determinant)				
Diater MDM (minor determinant) (if available)				
Ampicillin 20-25mg/ml OR amoxicillin 20-25mg/ml				
Penicillin 10 000 U/ml (if available)				

13. APPENDIX 2 – 1 AND 3 MONTHS FOLLOW-UP TELEPHONE QUESTIONNAIRE - TELEPHONE SURVEY SCRIPT [29]

Telephone survey script

Verbal consent script for patients who were randomized in the trial.

"Hello could I please speak to (patient's full given name and surname)?"

Hello, I am _____, (name and function in the hospital). You have participated in a study on Penicillin allergy, the PROSPECTOR Study, about 1 month (or 3 months) ago. We are now contacting you for the second part of the study in order to find out what antibiotics you have used after the antibiotic allergy testing at our center (Name the center) or any side effects. You have been selected to be involved in this project because you came to our center and had your antibiotic allergy reviewed.

Before we proceed further, can I please confirm your full name and date of birth?

If you agree to continue to participate in this study, we will ask you some questions about your allergies and what antibiotics you have taken and any problems with your antibiotics recently. Usually, the interview takes about 10 minutes, but if we identify some problems with your allergies and we help you to solve these problems, it might take longer. If we identify some problems, we might ask for your permission to contact your local doctor or the antibiotic allergy service at our center that can help you to solve these problems. Taking part in this interview is completely voluntary and will not affect your future care at our center.

If the patient is not at home:

"Is there a time that I could call back to speak with (patient's name)?"

If the patient is busy:

"Is there another time that I could call back that would be convenient?"

Patient questions

Do you consent for us to check what antibiotics you have been prescribed by your doctors in the community and dispensed by your pharmacy? We can check this via a program called (name the local program depending on the center).

1. What was the result of your penicillin oral challenge?
1. Penicillin allergy removed
2. Penicillin allergy confirmed
3. I don't know

2. Did you have any reaction to oral challenge after the 7-day observation period?
If Yes, state reaction:

2.1. What treatment was required? (eg, General Practitioner visit, antihistamines, topical steroids, readmission to hospital)

3. Have you received an antibiotic since the test?
3.1. If yes, what was the name of the antibiotic?
If unable to recall, prompt: Was it a "penicillin"?

3.2. If yes (ie, penicillin received), did you have any reaction to the penicillin?

3.3 If yes, did the doctors indicate that you had an infection resistant to penicillins that required broad spectrum antibiotics?

3.5. If yes, following your antibiotic course, were you diagnosed with serious diarrhoea or a C. difficile infection?

4. Did you receive a letter about your allergy post-testing? Y/N

5. Do you feel you know more about penicillin allergies? Y/N

6.. Do you feel you know more about your reactions to penicillin? Y/N

7. Are you still avoiding penicillin(s)?

If Yes, please explain why? Free-text (Investigator to categorize later)

8. Did you consider yourself allergic to penicillin? Y/N

If Yes, the next time you are admitted to hospital, would you say that you are allergic to penicillin?

9. Do you have any comments about the testing, either good or bad, that you would like to pass on to the team? [freetext]

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