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| Oral penicillin provocation in low risk penicillin allergies – ORACLE Study |
| Protocol Number: ORACLE1  Version: 5  Date: 16/06/2020 |
|  |
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| **Study Synopsis** |  |

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| --- | --- |
| Title: | Oral penicillin provocation in the Intensive Care Unit (ICU) |
| Short Title: | ORACLE Study |
| Design: | Single center pilot feasibility randomised controlled trial |
| Study Centre: | Austin Health |
| Hospital: | Austin Hospital |
| Study Question: | Is oral penicillin provocation in patients with an identified low risk penicillin allergy feasible and safe in the ICU setting |
| Primary Objectives: | To investigate the feasibility and safety of oral penicillin provocation in patients admitted to the ICU   * Eligibility to screened patient ratio * Recruitment to eligibility ratio * Protocol compliance * Safety-related concerns – adverse events |
| Secondary Objectives: | Exploratory efficacy outcomes   * Utilization of any penicillin during ICU stay * Utilization of any narrow spectrum beta-lactam during ICU stay * Utilization of vancomycin during ICU stay * Utilization of any restricted antibiotic during ICU stay * Utilization of any penicillin during hospital admission * Utilization of any narrow spectrum beta-lactam during hospital admission * Utilization of vancomycin during hospital admission * Utilization of any restricted antibiotic during hospital admission * In-Hospital mortality * ICU length of stay and hospital length of stay |
| Inclusion Criteria: | 1. A low or moderate penicillin allergy phenotype with a PEN-FAST score < 3 2. Are expected to stay in the ICU at least 24 hours from time of initial assessment |
| Exclusion Criteria: | 1. Patient age is < 18 years 2. Pregnancy 3. DNR (do not resuscitate) DNI (do not intubate) orders 4. Death is deemed imminent or inevitable during this admission, and either the attending physician, patient or substitute decision-maker is not committed to active treatment 5. Any other illness that, in the investigator’s judgement, will substantially increase the risk associated with subject’s participation in this study 6. Patients with known history of drug-associated anaphylaxis 7. Patients with idiopathic urticaria/anaphylaxis or mastocytosis 8. Patients where the allergy history was not able to be confirmed with patient or substitute decision maker 9. Patients on antihistamine therapy (excluding ranitidine) 10. Patients on adrenaline or noradrenaline therapy in last 4 hours 11. Patients receiving more than stress dose steroids (i.e. > 50mg QID hydrocortisone [or steroid equivalent]) 12. High ventilator requirement if intubated (any of the following)     * 1. Any mode other than spontaneous       2. Peak end expiratory pressure (PEEP) >5cm H2O       3. FiO2 >40% |
| Number of Subjects: | 80 |
| Investigational product: | Not applicable |
| Safety considerations: | Serious adverse event as per definition  Antibiotic associated immune mediated adverse event as per definition |
| Statistical Methods: | Statistical analysis will be performed using commercial statistical software, with a p value of 0.05 to indicate statistical significance. Outcomes will be compared after log transformation where appropriate. Comparisons will be made using t-test and ANOVA for repeated-measures or Wilcoxon rank-signed test and Kruskal-Wallis according to the underlying distribution for continuous data and Chi-square for categorical data.  When there are baseline imbalances, logistic regression analysis will also be performed to adjust for them. Analysis will be on an intention-to-treat basis. |
| Subgroups: | Nil |

## **Glossary of Abbreviations & Terms**

|  |  |
| --- | --- |
| **Abbreviation** | **Description (using lay language)** |
| De-labelled | The removal of a patients reported allergy if no adverse event is noted following direct oral provocation or re-challenge with implicated drug |
| Oral provocation | The provision of a test dose of drug to prove or disprove allergy |
| NSP | Narrow spectrum penicillin |
| NSB | Narrow spectrum beta-lactam |
| PEN-FAST | Penicillin allergy decision rule |
| ICU | Intensive care unit |

## **Study Sites**

### Study Location/s

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Site** | **Address** | **Contact Person** | **Phone** | **Email** |
| Austin Health | 145 Studley Road, Heidelberg VIC 3084 | A/Prof Jason Trubiano | (03) 94966709 | Jason.trubiano@austin.org.au |

## **Introduction/Background Information**

### Lay Summary

Penicillin allergies are a major burden on patients and hospitals. Currently, up to 1 in 4 Australian patients admitted to hospital will report an antibiotic allergy, many of which limit appropriate antibiotic usage and lead to inferior health outcomes. In many instances, patients will report what is considered a “low-risk” penicillin allergy and are appropriate for a penicillin re-challenge (i.e. a simple test dose) to determine if they are still allergic. We have developed assessment tools and a protocol for performing this test dose which has been safe and effective in over 98% of Austin inpatients. However, at present the safety and efficacy of performing oral penicillin re-challenge in the ICU setting is unknown, despite significant potential benefits to patients. This study will determine if penicillin oral re-challenge can be feasibly and safely performed in a small number of ICU patients to allow for future studies to examine the potential benefits of such testing in a larger group of patients.

### Introduction

Penicillin allergies are highly prevalent in the hospital setting and Intensive Care Unit (ICU) and associated with inferior antibiotic prescribing. Over 50% of reported penicillin allergies are considered low risk and can be identified via validated antibiotic allergy assessment tools and removed (i.e. de-labelled) via point-of-care single test dose provocation (i.e. re-challenge). However, the safety and efficacy of antibiotic allergy assessment followed by oral penicillin provocation in the ICU is unknown. This study aims to answer the question whether the removal of penicillin allergy in the ICU setting via direct oral penicillin provocation (i.e. test dose) is safe and improves utilization of penicillin-based antibiotic therapies via a pilot randomised controlled trial.

### Background information

Patient-reported penicillin allergies result in poor health outcomes for patients and drive inappropriate antibiotic prescribing, antimicrobial resistance and healthcare costs.1-5 Critically ill patients, such as those in the intensive care unit (ICU), are especially vulnerable to the impact of penicillin allergies,6, 7 yet have been poorly represented in interventional de-labelling programs. This impact is magnified, as the prevalence of penicillin allergies is highest in the critical care setting (9-15%),1 with 50% of these considered low risk and amenable to point-of-care de-labelling.3 **Despite the described burden of low-risk penicillin antibiotic allergies being highest in the ICU setting, these have not been addressed in controlled interventional studies.**

We recently demonstrated in an Australian ICU that antibiotic allergies are associated with inferior prescribing, in particular the excessive utilization of vancomycin (aOR 2.04; 95% CI 1.07, 3.86) and inadequate use of narrow spectrum beta-lactams (aOR 0.52; 95% CI 0.29, 0.94)5. In a range of observational studies that have included ICU patients, penicillin allergies are associated with the increased use of restricted antibiotics.5 **There is strong evidence to suggest that the presence of a penicillin allergy is associated with the use of non-preferred and broad-spectrum antibiotics.**

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 provocation (i.e. test dose in non-ICU hospitalized patients).9 However, the safety and efficacy of oral provocation in critical care is ill defined.5 Moran *et al*. demonstrated that penicillin allergy testing in the ICU was associated with increased use of narrow spectrum antibiotics and decreased utilization of restricted antimicrobials.5 In this single centre study at Austin Health narrow spectrum beta-lactams were utilized in 39.5% in patients reporting any antibiotic allergy compared with 58.8% without (p=0.028). However traditional penicillin allergy skin testing in the ICU has challenges, including false negatives and requires intensive resources.5 We have demonstrated the safe use, in the inpatient setting, of an antibiotic allergy assessment tool and point-of-care direct oral provocation (n=196, 98.9% efficacy- Chua *et al*. Antibiotic Allergy De-Labelling project 201910). A recent unmatched single centre cohort study demonstrated the safe administration of single-dose direct amoxicillin challenge in ICU patients with low-risk penicillin allergy (n=54, 100% uncomplicated).16 Further, our group has internally and externally validated a novel penicillin allergy clinician decision rule (PEN-FAST) that is able to identify low risk penicillin allergies with a negative predictive value (NPV) of 96% (95% CI 94-98%)11. **Therefore, whilst validated tools exist to enable inpatient penicillin assessment and de-labelling, limited evidence is available regarding the safety and efficacy in the ICU setting.**

## **Study Objectives**

### Hypothesis

That direct oral penicillin provocation in ICU patients identified as having a low-risk penicillin allergy is safe and feasible.

### Study Aims

To investigate the feasibility, safety and acceptability of oral penicillin provocation in ICU patients that report a penicillin allergy

### Outcome Measures

**Feasibility outcome measure:**

1. Proportion of patients assessed that are eligible for intervention (i.e. randomisation) as per protocol [Eligibility to screened ratio]
2. Feasibility of recruitment defined as the proportion of patients consenting to participation in the study as per protocol from eligible patients. [Recruitment to eligibility ratio].
3. Feasibility of intervention delivery defined as the proportion of patients randomised to the intervention arm who had the intervention delivered as per protocol. [Intervention to recruitment ratio]

**Safety outcome measures:**

* Safety: The proportion of patients with a penicillin allergy who experience an antibiotic associated immune mediated adverse event OR severe adverse drug reaction as per protocol definitions.
* Protocol compliance
* Exploratory efficacy outcomes
  + Utilization of any penicillin during ICU stay
  + Utilization of any narrow spectrum beta-lactam during ICU stay
  + Utilization of vancomycin during ICU stay
  + Utilization of any restricted antibiotic during ICU stay
  + Utilization of any penicillin during hospital admission
  + Utilization of any narrow spectrum beta-lactam during hospital admission
  + Utilization of vancomycin during hospital admission
  + Utilization of any restricted antibiotic during hospital admission
  + In-Hospital mortality
  + ICU length of stay and hospital length of stay

# **Definitions**

**De-labelled -** The removal of a patients reported allergy if no adverse event is noted following direct oral provocation or re-challenge with implicated drug.

**Feasibility of recruitment** – 50% for eligibility to screened ratio

**Feasibility of intervention** - 85% for recruitment to eligibility ratio

**Penicillin allergy label** – A patient reporting an allergy to any of: penicillin “Unspecified”, penicillin VK, penicillin G, amoxicillin, ampicillin, flucloxacillin, dicloxacillin.

**Narrow spectrum penicillin (NSP):** Penicillin VK, penicillin G, amoxicillin, ampicillin, flucloxacillin, dicloxacillin.

**Narrow spectrum beta-lactam**: NSP + cefazolin and cephalexin.

**Restricted antimicrobial agents**: cefepime, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, meropenem, moxifloxacin, piperacillin/tazobactam, teicoplanin, tobramycin and vancomycin.

**Cephalosporin allergy**: Reported allergy to any of: cephalexin, cefuroxime, cefaclor, cefazolin, ceftriaxone, cefepime, ceftazidime.

**Low risk penicillin allergy** – Unknown > 10 years, maculopapular rash (MPE) greater than 10 years prior, Type A adverse drug reaction (ADR) as per published definition12, local injection site reaction, childhood benign exanthema.

**Oral penicillin provocation (challenge)** – As per published protocols.9 In brief, following informed consent 250mg amoxicillin (orally) given to patients and patient observed for 2 hours post dose. Baseline and 30 min observations until 2 hours post dose. Emergency medications to be made available on site (including EPIPEN).

**Negative oral penicillin provocation (challenge)** – No antibiotic associated adverse event including allergy.

**Guideline preferred beta-lactam antibiotic –** Preferred beta-lactam antibiotic as stipulated by hospital guideline or Australian Therapeutic Guidelines (if no local guideline available).

**Antibiotic Associated Immune Mediated Adverse Event** - Any immune mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocation judged by two independent reviewers

**Serious Adverse Event:** Any one of the following causally related to study intervention;

* + - 1. Results in death,
      2. Is life-threatening
      3. Requires inpatient [hospitalisation](https://en.wikipedia.org/wiki/Inpatient_care) or causes prolongation of existing hospitalization
      4. Results in persistent or significant disability/incapacity,
      5. Is a congenital anomaly/birth defect, or
      6. Requires intervention to prevent permanent impairment or damage

# **Study Design**

### Study Type & Design & Schedule

This is a pilot, feasibility, single centre, randomised clinical trial (Summary in **Figure 1**) to be conducted in the ICU of Austin Hospital. We will include 80 patients and allocate them 1:1 ratio to the intervention group (oral penicillin provocation) and control group (standard of care). In greater detail - Eligible patients admitted to the ICU reporting a penicillin allergy will be identified from a daily electronic medical record (EMR) generated list by study investigators. Patients will be assessed by study investigators utilizing a validated Antibiotic Allergy Assessment Tool (**Appendix 1**).¹³,¹⁴ If the Antibiotic Allergy Assessment Tool identifies a low or moderate risk penicillin allergy phenotype the PEN-FAST clinical decision rule will be applied (**Appendix 2**). Informed written consent will be sought from those with a PEN-FAST score < 3 and they will be randomised to the intervention arm or standard of care.

*Intervention:*

The intervention is 250mg of oral amoxicillin\* (capsule or liquid via enteral route, including nasogastric) following baseline observations being performed (i.e. temperature, heart rate, blood pressure, respiratory rate, skin check). The amoxicillin test doses will be charted by the study clinician following approval by the treating ICU clinician and admitting unit (review of baseline observations) and administered via bedside nursing staff. Patients in the intervention arm will have the same observations performed by the beside nursing staff at +30, +60, +90 and +120 minutes post oral provocation. If at any stage an antibiotic associated adverse event is noted the treating and study clinicians will be informed and treatment of the adverse event will be at the discretion of the treating clinician*.* If patients are randomised to the intervention arm they will also undergo a repeat single-dose oral amoxicillin (250mg) provocation at least 48 hours post initial provocation, if they remain an inpatient. The repeat challenge is to ensure that a false negative oral provocation secondary to critical illness did not occur with the first challenge. Patients will be reviewed post each provocation at 24 hours and 5 days, and at 90 days post randomisation [in person if inpatient or alternatively via phone if discharged] for any serious or antibiotic-associated adverse events as per protocol definitions

*\*If the primary reported allergy is flucloxacillin or dicloxacillin then the implicated drug will be administered instead of amoxicillin at a dose of 250mg.*

*Control:*

Routine management as per the treating clinicians without oral penicillin provocation as per published protocol. Patients in the control arm will have observations performed by the beside nursing staff at +30, +60, +90 and +120 minutes post randomisation. Patients will be reviewed at 24 hours and 5 days post-randomisation, 24 hours and 5 days post discharge and 90 days post randomization for any serious or antibiotic-associated adverse events as per protocol definitions.

There will be no additional blood sampling or testing for patients in either arm of the trial.

**The ICU and treating clinicians will be blinded to the formal Antibiotic Allergy Assessment Tool result and PEN-FAST score. The ICU and treating clinicians will not however be blinded to the result of eligibility to be randomized (i.e. low risk vs. high risk) or the outcome of the oral penicillin provocation.**

## **Figure 1** – Overview of ORACLE study design

*A screenshot of a cell phone

Description automatically generated*

### Randomisation

Randomisation will be by means of sequentially numbered sealed envelopes utilising permuted blocks of variable size. Each envelope will contain a study arm allocation.

## Study methodology

All eligible patients who have a low or moderate penicillin allergy phenotype on Antibiotic Allergy Assessment Tool (Appendix 1) and PEN-FAST score < 3 will be randomised to receive either:

Oral amoxicillin 250mg single dose\* following by routine observations for 2 hours

**OR**

No oral penicillin provocation

*\*If the primary reported allergy is flucloxacillin or dicloxacillin then the implicated drug will be administered instead of amoxicillin at a dose of 250mg. A second single-dose oral challenge will be administered prior to discharge if the patient remains an inpatient >48 hours post-initial challenge.*

**Once randomized the patient can receive the oral penicillin provocation at any time during the ICU admission (at convenience of the ICU physicians).**

## **Study Population**

### Recruitment Procedure

All adult patients who have been admitted to the Department of Intensive Care, Austin Hospital and have a documented or reported penicillin allergy will be screened by ICU or Drug and Antibiotic Allergy Research staff for eligibility. If patient meets the eligibility criteria patients will be assessed for penicillin allergy phenotype by Infectious Diseases Department research staff utilizing the validated Antibiotic Allergy Assessment Tool13 (**Appendix 1**) and PEN-FAST scoring algorithm14 (**Appendix 2**). Those with a PEN-FAST score < 3 will be eligible for enrolment and randomization to oral penicillin provocation or standard of care.

### Inclusion Criteria

1. A PEN-FAST score < 3
2. Are expected to stay in the ICU at least 24 hours post assessment

### Exclusion Criteria

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

1. Patient age is < 18 years
2. Pregnancy
3. DNR (do not resuscitate) DNI (do not intubate) orders
4. Death is deemed imminent or inevitable during this admission, and either the attending physician, patient or substitute decision-maker is not committed to active treatment
5. Any other illness that, in the investigator’s judgement, will substantially increase the risk associated with subject’s participation in this study
6. Patients with known history of ANY drug-associated anaphylaxis
7. Patients with a known history of idiopathic urticaria, idiopathic anaphylaxis or mastocytosis
8. Patients where the allergy history was not able to be confirmed with patient or medical treatment decision maker
9. Patients on antihistamine therapy (excluding ranitidine)
10. Patients on adrenaline or noradrenaline therapy in last 4 hours
11. High ventilator requirement if intubated (any of the following)
    1. Any mode other than spontaneous
    2. Peak end expiratory pressure (PEEP) >5cm H2O
    3. FiO2 >40%
12. Patients receiving more than stress dose steroid therapy (i.e. > 50 mg QID hydrocortisone or daily equivalent)

**Patients initially ineligible due to points 8, 9, 10 or 11 may be able to be randomised at a later point in their ICU admission if the exclusion criteria have resolved.**

### Consent

All patients or their medical treatment decision maker screened for eligibility will be provided with a verbal explanation of the project. They will also be provided with the informed consent form. If required, consent will be obtained from the patient’s medical decision maker in person or over the telephone (verbal consent). If requested, a copy of the PICF will be given to the patients to further discuss with their treating medical team or family. Patients will be followed up by the study investigators in the ICU.

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

### Data collection

For all patients, data will be collected during the study by investigators as per the Case Record Form (REDcap) from the following data fields outlined below:

1. **Baseline demographics** (for each patient)
   1. Age, sex, age adjusted Charlson comorbidity index (CCI), admitting unit, immunosuppression history (prolonged steroid treatment defined as being on prednisolone or equivalent of > 10mg day for 1 month, cancer, haematological malignancy, autoimmune/rheumatological disorder requiring immunosuppression, transplant recipient, immune-uncontrolled HIV defined as CD4+ <200), chronic co-morbidities, APACHE-II score (at ICU admission)
   2. Baseline observations and Sequential organ failure assessment (SOFA) score at time of randomization and observations post-randomisation (control) or provocation (intervention)
   3. Any vasopressor utilization during ICU admission for > 24 hours continuous duration
2. **Allergy history – Medical record and Enhanced assessment output**
   1. Listed antimicrobial(s) in allergy section of EMR
   2. Listed allergy description in allergy section of EMR
   3. Any antibiotic allergy testing performed during study period
   4. Antibiotic allergy phenotype (**risk and type**) from Antibiotic Allergy Assessment Tool (Appendix 1)
   5. PEN-FAST parameters and score (Appendix 2)
   6. Previous infective episode/colonization (last 90 days)
3. Vancomycin resistant Enterococcus (VRE) colonization status (Y/N), date
4. Methicillin sensitive *Staphylococcus aureus* (MSSA)/Methicillin resistant *Staphylococcus aureus* (MRSA) colonization status (Y/N), date
5. Multi-drug resistant gram-negative colonization (Y/N), date
   1. Infective episodes and antibiotic utilization during index ICU admission and post ICU admission date (until day 90 post randomisation) as per Centre for Disease Control (CDC) definitions
      1. Antibiotics: Dose, frequency, duration, route, date/time of administration, time of administration (including surgical antibiotics)
      2. Antibiotics: National Antibiotic Prescribing Survey (NAPS) appropriateness score (1 or 2, appropriate vs. 3 or 4, inappropriate) assigned by two independent reviewers blinded to intervention, with prior credentialing in adjudging scores by NAPS online module.15 Excluded from the NAPS appropriateness score is the component judging a prescription appropriate if recommended by an ID physician or microbiologist.
   2. **Adverse drug reactions**
      1. Definition – *Serious Adverse Event*: Any one of the following causally related to study intervention;
6. Results in death,
7. Is [life-threatening](https://en.wikipedia.org/wiki/Death)
8. Requires inpatient [hospitalisation](https://en.wikipedia.org/wiki/Inpatient_care) or causes prolongation of existing hospitalization
9. Results in persistent or significant disability/incapacity,
10. Is a congenital anomaly/birth defect, or
11. Requires intervention to prevent permanent impairment or damage
    * 1. Definition – *Antibiotic Associated Immune Mediated Adverse Event*
12. Any immune mediated [immediate (IgE) or non-immediate (T-cell)] reaction as judged by two independent reviewers
13. **Penicillin provocation details**
    * 1. If oral penicillin provocation performed as per protocol
      2. If any penicillin provocation (test dose or IV) performed not per protocol
      3. For all provocations
         1. Agent, dose, duration, frequency, date
14. **Admission details**
15. Admission date, discharge date, length-of-stay (days)
16. ICU Admission date, discharge date, length-of-stay (days)
17. Transfer from another hospital
18. Mortality (inpatient) – all-cause and attributable (infection-related or adverse drug reaction-related)
19. Mortality (30-day) – all-cause and attributable (infection-related or adverse drug reaction-related)

# **Participant Safety and Withdrawal**

### 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, 13, 14 The Antibiotic Allergy Assessment Tool and oral penicillin protocol are now standard of care in all hospital wards outside of the ICU. 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.

### Handling of Withdrawals

Participants may withdraw from the study at any point for the following reasons: the participant has chosen to withdraw from the study, or a protocol violation has occurred. In these circumstances, the participants will be removed from analysis.

### Replacements

Upon withdrawal of an enrolled participant, another participant will be recruited and randomised through the central allocation system. The study will conclude when at least 80 patients are enrolled, with at least 40 cases in each arm.

### Serious adverse events

SAEs are defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) as any untoward medical occurrence that:

* Results in death
* Is life-threatening
* Requires inpatient hospitalisation or prolongation of existing hospitalisation
* Results in persistent or significant disability/incapacity
* Is a congenital anomaly/birth defect
* Is an important medical event which may require intervention to prevent one of the previously listed outcomes

### Reporting

SAEs that occur from the time of commencement of study treatment to 5 days post-hospital discharge will be collected and reported to the Austin Health Human Research Ethics Committee and to the DSMC within 24 hours of study staff becoming aware of the event.

Minimum information to report will include:

• Patient initials and study number

• Nature of the event

• Commencement and cessation of the event

• An investigator’s opinion of the causal relationship between study involvement and the event (unrelated, possibly, probably or definitely related).

• Whether treatment was required for the event and what treatment was administered.

# **Statistical Methods**

### Sample Size Estimation & Justification

This is a pilot feasibility and safety study and it is designed to allow subsequent power calculation for future trials as well as feasibility. As the primary outcome of the study is proportion of patients with their penicillin allergy de-labelled following randomization, we believe that a study of 80 patients would provide sufficient exposure to the study protocol to achieve a sufficiently preliminary assessment of effect of oral penicillin provocation. Forty will be allocated to oral penicillin provocation and the other forty to the standard of care arm.

### Power Calculations

This sample size is feasible, as we assume that 9% of all screened patients will report a penicillin allergy as per national data1, and in an observational study by Moran *et al*. in Austin Health ICU6 200 patients would be expected to be eligible in an 12 month study period. Assuming a 50% recruitment and 85% actually receive the intervention post randomization, this would generate a projected total sample size of 85 patients.

Assuming 1:1 randomization between two study arms, this will provide sufficient precision for both feasibility and safety outcomes.

### Statistical Methods To Be Undertaken

Data analysis will be performed on an intention-to-treat basis as well as per protocol. Summary statistics will be used to describe the clinical data and presented as mean ± SD, median with interquartile range (IQR) or percentages as appropriate.

Feasibility and safety outcomes will be reported as percentage with 95% confidence intervals. Logistic regression will be used to compare antibiotic utilization and mortality between groups. Results will be reported as odds ratios with 95% confidence intervals. Negative binomial regression will be used for comparison of length of stay (reported as incidence rate ratio with 95% CI). Level of statistical significance will be set at 0.05 or less. Results will be reported according to CONSORT guidelines.

# **Data Security & Handling**

### Details of where records will be kept & How long will they be stored

Investigators will design the data collection forms. Patient clinical details and demographics will be recorded on these as well. Completed forms will be kept in the Department of Infectious Diseases at Austin hospital. The collected data from the Austin Hospital’s computerised laboratory results, patients’ EMR (e.g. Scanned medical record and Cerner) will then be stored on an electronic database (i.e. REDcap Austin Health) on password-protected computers located within the Infectious Diseases Department at Austin Hospital. Paper data and study related documents used in this study will be de-identified and only a master log will be maintained to identify participants and their study data. The log will be locked in a protected office. All data for study will be retained for a period of fifteen years after which all electronic and paper data will be destroyed in accordance with 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 critically ill patients, 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.

### Confidentiality and Security

This is an investigator-initiated practice change study being conducted at the Austin Hospital, Australia and does not have a data and safety management committee.

### Ancillary data

Not applicable to this pilot randomization control trial.

# **References**

1. Trubiano JA, Chen C, Cheng AC, Grayson ML, Slavin MA, Thursky KA, et al. Antimicrobial allergy 'labels' drive inappropriate antimicrobial prescribing: lessons for stewardship. J Antimicrob Chemother 2016; 71:1715-22.

2. MacFadden DR, LaDelfa A, Leen J, Gold WL, Daneman N, Weber E, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. Clin Infect Dis 2016; 63:904-10.

3. Trubiano JA, Pai Mangalore R, Baey YW, Le D, Graudins LV, Charles PG, et al. Old but not forgotten: Antibiotic allergies in General Medicine (the AGM Study). Med J Aust 2016; 204:273.

4. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. BMJ 2018; 361:k2400.

5. Moran R, Devchand M, Smibert O, Trubiano JA. Antibiotic allergy labels in hospitalized and critically ill adults: A review of current impacts of inaccurate labelling. Br J Clin Pharmacol 2019; 85:492-500.

6. Moran R, Devchand M, Churilov L, Warrilow S, Trubiano JA. The burden of antibiotic allergies in adults in an Australian intensive care unit: the BASIS study. Critical Care and Resuscitation 2019.

7. Trubiano JA, Grayson ML, Thursky KA, Phillips EJ, Slavin MA. How antibiotic allergy labels may be harming our most vulnerable patients. Med J Aust 2018; 208:469-70.

8. Trubiano JA, Thursky KA, Stewardson AJ, Urbancic K, Worth LJ, Jackson C, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. Clin Infect Dis 2017; 65:166-74.

9. Trubiano JA, Smibert O, Douglas A, Devchand M, Lambros B, Holmes NE, 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.

10. Chua KY, Vogrin S, Holmes NE, Douglas A, Tan N, Trubiano JA. Whole of hospial penicillin allergy assessment oral provocation healthservices study - Antibiotic Allergy Discovery and De-labelling Program (AADDP). 2009.

11. Trubiano JA, Vogrin, S., Chua, K.Y., Holmes, N.E., Phillips, E.J. PEN-FAST - A validated penicillin allergy clinical decision rule 2019.

12. Rawlins MD TJ. Textbook of adverse drug reactions. Oxford: Oxford University Press; 1977.

13. Devchand M, Urbancic KF, Khumra S, Douglas AP, Smibert O, Cohen E, 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 e5.

14. Trubiano J, Vogrin S, Holmes NE, Chua K, Douglas A, Bourke J, et al. Development and validation of a penicillin allergy clinical decision rule. JAMA Internal Medicine. 2020. doi:10.1001/jamainternmed.2020.0403.

15. NAPS - National Antimicrobial Prescribing Survey. 2015.] Available from <https://naps.org.au/>.

16. Stone C, Stollings J, Lindsell C, Dear M, Buie R, Rice T, Phillips E. Risk-stratified management to remove low-risk penicillin allergy labels in the intensive care unit. AJRCCM. 2020. doi:10.1164/rccm.202001-0089LE

# **Appendix 1 – Antibiotic Allergy Assessment Tool**

**Penicillin allergy assessment questions**

1. What is the name of the oral penicillin?

Penicillin unspecified □ Penicillin VK **□** Penicillin G **□** Amoxicillin **□**

Ampicillin □ Dicloxacillin **□** Flucloxacillin **□** Nafcillin **□**

Oxacillin □ Benzathine **□** Amoxicillin clavulanate **□**

1. Please describe the detailsof this reaction. (*see descriptions in tool)*
2. How many years ago did the reaction occur?

More than 5 years ago? Yes **□** No **□**

More than 10 years ago? Yes **□** No **□**

1. How long after having the first antibiotic dose did the reaction occur?

Immediate (within 1-2 hours)? Yes **□** No **□**

1. Did it require any systemic treatment?

Yes **□** No **□**

1. Were you hospitalised as a result of this reaction? Yes **□** No **□**

A screenshot of a cell phone

Description automatically generated

# **Appendix 2 – PEN-FAST**

*A screenshot of a cell phone

Description automatically generated*

† Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Drug Reaction with Systemic Symptoms, Acute Generalized Exanthematous or blistering or desquamating rash potentially consistent with SCAR.

‡ or unknown