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The use of a penicillin allergy clinical decision rule to enable direct oral penicillin provocation: an international multicenter randomized control trial (PALACE)

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ABSTRACT

Introduction

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. More than 85% of all penicillin allergy labels can be removed by skin testing [1] and 96-99% of low-risk penicillin allergy labels can be removed by direct oral challenge [2-4]. An internally and externally validated clinical assessment tool for penicillin allergy, PEN-FAST, can identify a low-risk penicillin allergy without the need for skin testing; a score of less than 3 has a negative predictive value (NPV) of 96.3% (95% CI, 94.1-97.8) for the presence of a penicillin allergy [5]. It is hypothesized that PEN-FAST is a safe and effective tool for assessing penicillin allergy in an outpatient clinic setting.

Methods and analysis

This is an international, multicenter randomized control trial using the PEN-FAST tool to risk-stratify penicillin allergy labels in adult outpatients. The study's primary objective is to evaluate the non-inferiority of using PEN-FAST score-guided management with direct oral challenge compared with standard care (defined as prick and intradermal skin testing followed by oral penicillin challenge). Participants will be randomized 1:1 to the intervention arm (direct oral penicillin challenge) or standard of care arm (skin testing followed by oral penicillin challenge, if skin testing is negative). The sample size of 380 randomized patients (190 per treatment arm) is required to demonstrate non-inferiority.

Ethics and dissemination

The study will be performed according to the guidelines of the Helsinki Declaration [6] and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia, Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605). The results of this study will be published and presented in various scientific forums.

Keywords: Drug Hypersensitivity, Penicillin, Skin Tests, Drug Evaluation

Strengths and limitations of this study

- This is an international multicenter, prospective non-inferiority randomized clinical trial.
- The investigators will use a validated clinical tool, the PEN-FAST as part of the inclusion criteria in the study.
- In terms of the limitations, this study excludes the pediatric population, considering that the clinical tool PEN-FAST was validated in an adult population.
- The recruiting institutions are specialized drug allergy centers that offer skin testing as standard of care.
- Finally, the conclusions from this trial might not be generalizable beyond the enrolled study population considering that the participants that consent to participate in this trial could be different from those that decline consent.

1. INTRODUCTION

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. Patient-reported penicillin allergies and incorrect antibiotic allergy labels result in poor health outcomes for patients, including increased length of stay and mortality rate during hospitalization [7, 8], and drive inappropriate antibiotic prescribing and antimicrobial resistance, increase side effects from second-line antibiotics, and increase healthcare costs [9-13].

Work from our group has shown that more than 85% of all penicillin allergy labels can be removed by formal skin testing [1] and 96-99% of low-risk penicillin allergies can be removed by point-of-care oral challenge [2-4]. We have internally and externally validated a novel penicillin allergy clinician decision rule (PEN-FAST) that can identify low-risk penicillin allergies (**Figure 1**) [5]. In patients with a reported penicillin allergy (**PEN**), based on four allergy history criteria (time since reaction ≤5 years (**F**), anaphylaxis or angioedema (**A**), severe cutaneous adverse reaction (**S**), or whether treatment (**T**) was required for reaction), a **PEN-FAST** score of < 3 is associated with 96.7% negative predictive value [5]. A PEN-FAST score of less than 3 classified 460/622 (74%) patients as low-risk [5]. Seventeen (3.7%) of these patients had a positive penicillin allergy test. This was subsequently externally validated against a retrospective multicenter cohort of 945 outpatients from Australia and the USA with consistent results [5].

A prospective randomized controlled trial evaluating the safety of drug challenge in patients with a low-risk penicillin allergy patient group (defined as skin rash, hives, itching, or unknown reaction that occurred more than 10 years before the assessment and that did not require emergency medical attention) has been reported [14]. Specifically, the authors included 159 allergic patients in the randomization (1:1) and compared skin testing followed by drug challenge (if skin testing negative) versus a gradual 2-step direct challenge. They identified 3/79 patients (3.8%) with a positive challenge (immediate skin manifestations treated with antihistamines, no epinephrine use), showing that the challenge was a safe and effective alternative for delabelling penicillin allergy. Further, a pre-operative clinic used 3 criteria ((1) an allergy history of more than 15 years prior and either an unknown reaction, (2) a non-itchy rash or (3) a type A adverse drug reaction) to identify 119 low-risk patients from a cohort of 219 patients [15]. Among these, 55/56 (98%) patients were successfully delabelled (3 dose amoxicillin challenge 5mg/50mg/500mg at 20 min interval followed by a 3-day course of amoxicillin) with one patient developed a delayed exanthem [15]. Similar, 328 military recruits that reported penicillin or cephalosporin allergy were challenged to a single-dose direct oral challenge with amoxicillin (250 mg) [16]. Five (1.5%) demonstrated an adverse drug reaction without anaphylaxis and were treated with oral anti-histamine and intramuscular adrenaline (to prevent reaction progression) [16]. The remaining 323 participants also received an intramuscular dose of benzathine penicillin without any reported adverse reactions [16]. A prospective two-year inpatient delabelling study in an intensive care unit setting with 12-16% prevalence of penicillin allergy labels identified around 60% of penicillin allergy labeled patients as low-risk [4]. When challenged with amoxicillin, 203/205 (99%) tolerated their challenge leading to label removal, and only two cases (<1%) had rash that led to return of the allergy label after a challenge or subsequent treatment [3].

Direct drug challenges, including penicillin, have been increasingly used in the outpatient setting [17, 18]. However, no multicenter randomized control trial utilizing a validated risk assessment tool has been

undertaken to assess the safety of direct oral penicillin challenge in the outpatient setting. In our international multi-center cohort study, we will use the validated clinical tool, PEN-FAST, to determine if a direct oral penicillin challenge, where PEN-FAST score < 3, is safe and effective when compared with standard of care penicillin skin testing followed by oral penicillin challenge.

2. METHODS AND ANALYSIS

2.1. Study Design

This is an international multicenter, prospective, non-inferiority randomized clinical trial (**Figure 2**) to be conducted in the outpatient drug allergy services at Austin Health (Melbourne, Victoria, Australia), Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia), Royal Melbourne Hospital (Melbourne, Victoria, Australia), Vanderbilt University Medical Center (Nashville, Tennessee, United States), Duke University Medical Center (Durham, NC, United States), and McGill University Health Centre (Montreal, Quebec, Canada).

2.2. Eligibility criteria section

We will include adult patients (≥ 18 years) reporting a penicillin allergy label where the calculated PEN-FAST score is less than 3. Participants will be excluded if they (1) present any illness that, in the investigator's judgment, will substantially increase the risk associated with their participation in this study, including neurological or psychological conditions; (2) have a history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis; (3) report an allergy history that cannot be confirmed; or (4) are on concurrent antihistamine therapy or receiving more than stress dose steroids (i.e.,> 50mg QID hydrocortisone or steroid equivalent). Pregnant patients will also be excluded from the study.

Potentially eligible patients referred to the outpatient clinic reporting a penicillin allergy will be identified and assessed with a standard clinical history and calculation of the PEN-FAST score (**Figure 1**). A penicillin allergy label will be defined as patients reporting an allergy to any of the following drugs: "unspecified," penicillin VK, penicillin G, amoxicillin, amoxicillin/clavulanate, ampicillin, flucloxacillin, or dicloxacillin.

2.3. Sample size and justification

The null hypothesis is that the difference in the proportion of positive allergy investigations, including drug provocation and skin testing, is not larger than 5 % (non-inferiority margin). To achieve 80% power, assuming the event rate in the control group is 4% and type 1 error probability of 5 % (one-sided), 380 patients need to be randomized (190 per group). Due to the randomization, intervention, and primary outcome being collected within the same visit, loss to follow-up is expected to be minimal.

2.4. Recruitment

Allergy outpatient clinics at the participating centers receive around 800 referrals per year for penicillin allergy patients. Thus, the authors estimate that recruitment will not represent an issue for this study. We

estimate that the recruitment period will be six months, excluding when the outpatients are closed due to institutional COVID-19 infection prevention-related policies.

2.5. Randomization

Participants meeting eligibility criteria will be randomized to either the intervention (direct oral penicillin provocation) or standard of care arm (skin testing followed by oral penicillin provocation if negative). Permuted block design randomization will be used, stratified by the hospital site. Randomization will be non-blinded and performed using REDCap (Research Electronic Data Capture). The allocation sequence will be developed and uploaded to REDCap by a trial statistician and will remain concealed.

2.6. Treatment Arms

Prior to the intervention or standard of care procedures, participants will be asked to complete a Drug Hypersensitivity Pre-Questionnaire (**Table 1**).

Table 1: Pre-Questionnaire

Please answer yes, no or non-applicable (N/A) to the following questions. **Mark the appropriate box with an x.** Veuillez répondre non, oui ou sans objet (N/A) aux questions suivantes.	**Yes Oui**	**No Non**	**N/A**
1. Would you like the allergist's/infectious disease's physician opinion before taking medications prescribed by other specialists? Souhaitez-vous l'avis de l'allergologue / de l'infectiologue avant de prendre des médicaments prescrits par d'autres spécialistes?	□	□	□
2. Do you talk to others about your allergy problem? Parlez-vous à d'autres personnes de votre problème d'allergie?	□	□	□
3. Is your family aware of your problem? Votre famille est-elle au courant de votre problème?	□	□	□
4. Is your partner conscious of your problem? Votre partenaire est-il au courant de votre problème?	□	□	□
5. Is your family doctor aware of your drug allergy problem? Votre médecin de famille est-il au courant de votre problème d'allergie aux médicaments?	□	□	□
6. Is your community pharmacist aware of your drug allergy problem? Votre pharmacien est-il au courant de votre problème d'allergie aux médicaments?	□	□	□
6. Would you be happy to have penicillin again in the community after a negative test result in clinic? Accepteriez-vous de recevoir à nouveau de la pénicilline dans la communauté après un résultat de test négatif en clinique?	□	□	□

The following questions concern the influence your drug allergy has on your quality of life. Answer every question by marking the appropriate box with an x. You may choose from one of the following answers.
Les questions suivantes portent sur l'impact de votre allergie médicamenteuse sur votre qualité de vie. Répondez à chaque question en cochant la case appropriée avec un x. Vous pouvez choisir parmi l'une des réponses suivantes.

0	**1**	**2**	**3**	**4**
Not at all	**Slightly**	**Moderately**	**Very**	**Extremely**
Pas du tout	Légèrement	Modérément	Très	Extrêmement

	0	1	2	3	4
6. Do you feel different from others? Vous sentez-vous different(e) des autres?	□	□	□	□	□
7. Do you feel unluckier from others? Vous sentez-vous moins chanceux (euse) par rapport aux autres?	□	□	□	□	□
8. Is it that even a little discomfort is a problem for you? Est-ce que même un peu d'inconfort est un problème pour vous?	□	□	□	□	□
9. Is your job efficiency affected by the problem of your allergy to medications? Votre efficacité au travail est-elle affectée par le problème de votre allergie aux médicaments?	□	□	□	□	□
10. Do you feel helpless? Vous sentez-vous impuissant(e)?	□	□	□	□	□
11. Do you sleep badly? Vous dormez mal?	□	□	□	□	□
12. Do you feel embarrassed in relationships with others? Vous sentez-vous gêné(e) dans vos relations avec les autres?	□	□	□	□	□
13. Since you are unable to take medications, does every illness limit you more than other people? Puisque vous êtes incapable de prendre des médicaments, est-ce que chaque maladie vous limite plus que les autres?	□	□	□	□	□
14. Do you have difficulties concentrating? Avez-vous des difficultés à vous concentrer?	□	□	□	□	□
15. Does your allergy problem interfere with your sexual life? Votre problème d'allergie interfère-t-il avec votre vie sexuelle?	□	□	□	□	□
16. Do you feel anguished due to your problem of allergy reaction? Vous sentez-vous angoissé à cause de votre problème de réaction allergique?	□	□	□	□	□
17. Do you feel ill? Vous vous sentez malade?	□	□	□	□	□
18. Are you restricted in your nutrition from fear of substances you might be allergic to? Êtes-vous limité(e) dans votre alimentation par peur de consommer substances auxquelles vous pourriez être allergique?	□	□	□	□	□
19. Are you afraid of being administered a medication during an emergency to which you are allergic? Avez-vous peur de recevoir un médicament auquel vous êtes allergique, en cas d'urgence?	□	□	□	□	□
20. Do you feel you can't cope with your allergy problem? Pensez-vous que vous ne pouvez pas faire face à votre problème d'allergie?	□	□	□	□	□
21. For each disease, would you be confident that there is a medication that you can safely take?	□	□	□	□	□

Pour chaque maladie, êtes-vous certain qu'il existe un médicament que vous pouvez prendre en toute sécurité?					
22. Are you afraid you could not deal with the pain? Avez-vous peur de ne pas pouvoir supporter la douleur?	☐	☐	☐	☐	☐
23. Do you feel anxious due to your problem of allergy reaction? Vous sentez-vous anxieux en raison de votre problème de réaction allergique?	☐	☐	☐	☐	☐
24. Does your problem influence your relationships with other people? Votre problème influence-t-il vos relations avec les autres?	☐	☐	☐	☐	☐
25. Are you in a bad mood due to your problem of allergy reaction? Êtes-vous de mauvaise humeur en raison de votre problème de réaction allergique?	☐	☐	☐	☐	☐
26. Do you feel frightened due to your problem of allergy reaction? Avez-vous peur à cause de votre problème de réaction allergique	☐	☐	☐	☐	☐
27. Do you worry every time you take a medication different from ones that cause your allergic reactions? Vous inquiétez-vous à chaque fois que vous prenez un médicament différent de ceux qui provoquent vos réactions allergiques?	☐	☐	☐	☐	☐
28. Do you feel tired during the day because you sleep badly at night? Vous sentez-vous fatigue(e) pendant la journée parce que vous dormez mal la nuit?	☐	☐	☐	☐	☐
29. Do you give up leisure activities (sport, vacations, trips) because of your problem? Avez-vous abandonné les activités de loisirs (sport, vacances, voyages) à cause de votre problème?	☐	☐	☐	☐	☐
30. Does the idea of taking a medicine make you feel anxious? L'idée de prendre un médicament vous rend-il anxieux(euse)?	☐	☐	☐	☐	☐
31. Are you annoyed by frequent medical controls? Êtes-vous agacé(e) par les contrôles médicaux fréquents?	☐	☐	☐	☐	☐
33. Does the problem of adverse reaction to medications affect your life? Le problème des réactions indésirables aux médicaments affecte-t-il votre vie?	☐	☐	☐	☐	☐
34. How likely are you to believe a negative penicillin allergy test result? Quelle est la probabilité que vous croyiez un résultat négatif au test d'allergie à la pénicilline?	☐	☐	☐	☐	☐
35. How likely do you think it is that your penicillin allergy test will be negative? Selon vous, quelle est la probabilité que votre	☐	☐	☐	☐	☐

test d'allergie à la pénicilline soit négatif?					

Intervention: Participants will receive a single dose of oral penicillin or penicillin derivatives in the intervention group after baseline vital sign assessment (i.e., temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, skin check). Nursing staff will repeat vital signs as needed after oral challenge while observing for signs of an immune mediated adverse reaction. The vital signs are also performed for all participants 60 minutes following the oral challenge. If an antibiotic-associated adverse event is noted at any stage, the standard of care treatment will be offered by the attending clinicians (e.g., epinephrine for immediate hypersensitivity reaction).

If the patient reports a reaction to either penicillin unspecified, penicillin G, penicillin V, semi-synthetic anti-staphylococcal penicillins, ampicillin, amoxicillin or amoxicillin/clavulanate, he/she will be administered either the implicated drug or amoxicillin, consistent with site local practice. The dose used for amoxicillin is 250 mg or the lowest available dose according to center availability. The implicated drug should also be administered at the lowest available dose. For the amoxicillin/clavulanate allergic patients, they will retain an allergy label to clavulanate.

Control: In the control group, routine management will include penicillin skin prick and intradermal beta-lactam inoculation adapted from previously published studies (**Table 2**) followed by oral penicillin challenge if skin testing is negative. Vital signs, observations, and management will be the same in both groups, and patients will be able to directly contact a member of the clinical team (phone or email) if any serious or antibiotic-associated adverse events (including non-immune mediated adverse events) occur in the 24 to 48 hours after oral provocation.

Table 2: DRUG ALLERGY TESTING CONCENTRATIONS

Skin Prick Testing (read at 15 minutes)
Histamine 10mg/ml
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Intradermal Testing (0.02 ml) (read at 15 minutes)
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Abbreviations: MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

Follow-up Telephone Questionnaire: A 6-month post-randomisation telephone questionnaire, based on previous publications [11], will help assess the impact of outpatient delabelling on patient perceptions of their allergy status (**Table 3**).

Table 3: Six months follow-up Questionnaire – Adapted from **[20]**

English
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 research team). You have participated in a study on Penicillin allergy, the PALACE Study, about six months ago. We are now contacting for the second part of the study to determine what antibiotics you have used after antibiotic allergy testing at our center, (*please complete with center name*). Before we proceed further, can I please confirm your full name and date of birth? Suppose you agree to continue participating in this study. In that case, 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 help you solve them, it might take longer. If we identify some issues, we might ask for your permission to contact your local doctor or (*please complete with physician name*) at the allergy service at our center that can help you solve these problems. Taking part in this interview is entirely voluntary and will not affect your future care at the (*please complete with center name*) or other hospitals. 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 remember having a test dose of penicillin in the outpatient clinic?** **If No**, do you agree to schedule a follow-up appointment with (*please complete with physician name)* to discuss the investigations at the outpatient clinic further? **If Yes**, please tell me whether you agree with these statements: 1. "I felt safe during the test dose."

a. Strongly agree
b. Agree
c. Neutral
d. Disagree
e. Strongly disagree

2. "I recommend the penicillin assessment to other patients with a penicillin allergy."
a. Strongly agree
b. Agree
c. Neutral
d. Disagree
e. Strongly disagree

3. What was the result of your penicillin assessment in the clinic?
a. Penicillin allergy removed
b. Penicillin allergy confirmed
c. I don't know

4. Did you have any late reaction to assessment after the observation period?
a. If Yes, state reaction:
b. What treatment was required? (e.g., General Practitioner visit, antihistamines, topical steroids, admission to hospital)

5. Have you received an antibiotic since the test?
a. If yes, what was the name of the antibiotic?
b. If unable to recall, prompt: Was a "penicillin"?
c. If yes (i.e., penicillin received), did you have any reaction to the penicillin?

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

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

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

9. Are you still avoiding penicillin(s)?

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

If No, Congratulations. We are happy to hear this. We will further continue with some questions.

10. Do you consider yourself allergic to penicillin? Y/N

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

b. Do you have any comments about the testing, either good or bad, for us?

If the patient states that they are **still avoiding penicillin** (Q9) or they consider **themselves allergic to penicillin** (Q10) and you have assessed them to be able to participate in a qualitative interview,

then say:

"We would like to explore these issues further. This would involve another phone interview. Would you be interested in participating? What would be a good time to call you?"

End—"That is the end of the questions. Thank you very much for your time."

French

Script d'enquête téléphonique

Consentement verbal pour les patients randomisés dans l'étude.

« Bonjour, pourrais-je parler à (nom et prénom complets du patient) ? »

Bonjour, je suis _____, (nom et fonction à l'hôpital). Vous avez participé à une étude sur l'allergie à la pénicilline, l'étude PALACE, il y a environ 6 mois. Nous vous contactons maintenant pour la deuxième partie de l'étude afin de savoir quels antibiotiques vous avez utilisé suite aux tests d'allergie dans notre centre, (nommer le centre).

Avant de poursuivre, puis-je confirmer votre nom complet et votre date de naissance ?

Si vous acceptez de continuer à participer à cette étude, nous vous poserons quelques questions sur vos allergies et les antibiotiques que vous avez pris ainsi que tout problème que vous auriez rencontré avec la prise d'antibiotiques récemment. Habituellement, l'entretien dure environ 10 minutes, mais si nous identifions certains problèmes liés à vos allergies et que nous vous aidons à résoudre ces problèmes, cela peut prendre plus de temps. Si nous identifions certains problèmes, nous pouvons vous demander la permission de contacter votre médecin local ou (nommer investigateur) au département d'allergie de notre centre qui peut vous aider à résoudre ces problèmes. La participation à cet entretien est entièrement volontaire et n'affectera pas vos futurs soins dans le (nommer le centre) ou autres hôpitaux.

Si le patient n'est pas à la maison :
« Y a-t-il un moment où je pourrais rappeler pour parler avec (nom du patient) ? »

Si le patient est occupé :
« Y a-t-il un autre meilleur moment quand je pourrais vous re-contacter?

Questions pour les patients

Vous souvenez-vous d'avoir eu une dose de pénicilline à la clinique externe?
Si Non, seriez-vous d'accord à organiser une rencontre de suivi avec (nommer l'investigateur)3 pour discuter les investigations que vous avez eu à la clinique d'allergie?

Si Oui, veuillez me dire si vous êtes d'accord avec ces affirmations :

2. "Je me sentais en sécurité pendant le test."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

2. "Je recommande l'évaluation de la pénicilline à d'autres patients allergiques à la pénicilline."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

3. Quel a été le résultat de votre évaluation concernant l'allergie à la pénicilline à la clinique ?
   a. Allergie à la pénicilline supprimée
   b. Allergie à la pénicilline confirmée
   c. Je ne sais pas

4. Avez-vous présenté une réaction retardée à l'évaluation après la période d'observation?
   a. Si oui, indiquez la réaction :
   b. Quels traitements ont été nécessaire ? (e.g.., visite chez le médecin généraliste, antihistaminiques, stéroïdes topiques, admission à l'hôpital)

5. Avez-vous reçu un antibiotique depuis le test ?
   a. Si oui, quel était le nom de l'antibiotique ?
   b. Si vous ne pouvez pas vous en souvenir, demandez : est-ce que c'était une « pénicilline » ?
   c. Si oui (c.-à-d. pénicilline reçue), avez-vous présenté une réaction à la pénicilline ?

6. Avez-vous reçu une lettre concernant votre allergie suite à l'évaluation? O/N

7. Avez-vous l'impression d'en savoir plus sur les allergies à la pénicilline? O/N

8. Avez-vous l'impression d'en savoir plus sur vos réactions à la pénicilline ? O/N

9. Évitez-vous toujours la (les) pénicilline(s) ?
Si oui, veuillez expliquer pourquoi ? Texte libre (le chercheur classera plus tard)

10. Vous considérez-vous allergique à la pénicilline ? O/N
Si oui, la prochaine fois que vous serez hospitalisé, diriez-vous que vous êtes allergique à la pénicilline ?
Si non, félicitations. Nous sommes heureux d'entendre cela. Nous allons continuer avec quelques questions.

11. Avez-vous des commentaires sur les tests, qu'ils soient bons ou mauvais, que vous aimeriez nous transmettre? [texte libre]

Si le patient déclare qu'il évite toujours la pénicilline (9) ou qu'il se considère allergique à la pénicilline (10) et que vous l'avez évalué pour pouvoir participer à un entretien qualitatif, alors dire:

« Nous aimerions approfondir ceci. Cela impliquerait un autre entretien téléphonique. Seriez-vous intéressé à participer? Quel serait le bon moment pour vous appeler ? »

Fin— « C'est la fin des questions. Merci beaucoup pour votre temps."

2.7. Adverse Events

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.

An antibiotic-associated immune-mediated adverse event will include any immune-mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocation judged by two independent reviewers. An antibiotic-associated adverse event will include any non-immune mediated reaction (e.g., nausea, vomiting, diarrhea) within 48 hours of oral provocation judged by two independent reviewers.

2.8. Withdrawals and Stopping Criteria

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. However, participants may request their data be destroyed if not already used in analysis. No withdrawals following randomization will be replaced.

2.9. Data management

Participants' clinical details and demographics will be recorded on electronic uniform data collection forms directly on REDCap. The collected data from every institution will then be stored on an electronic database on password-protected computers. The data from all recruiting sites will be hosted by a single REDCap database at the Austin Health. The participations sites will only have access to their locally entered patient data. A study monitor will be assigned at the Austin Health that will be responsible for data entry completion, error and consistency. According to the local institutional review board regulations, all data for this study will be retained. All electronic and paper data will be destroyed by hospital policy at the time.

2.10. Outcomes

The primary outcome is the difference in the proportion of patients with a positive oral challenge or positive skin testing (defined as an immune-mediated reaction).

Secondary outcomes are listed in **Table 4** and include (1) feasibility outcomes evaluating eligibility to screened ratio, the recruitment to eligibility ratio, and the intervention to recruitment ratio; (2) safety outcomes including protocol compliance and adverse reactions (antibiotic-associated immune-mediated adverse event or severe adverse drug reaction); and (3) efficacy outcomes. The efficacy outcomes are determined by the number of patients with non-immune reactions, the number of immediate and delayed positive skin testing. Other important elements are the time from randomization to delabelling, the number of appointments required for delabelling, participant's quality of life (**Table 4**) as well as measuring the impact on delabelling six months after the procedure (**Table 4**). In this context, delabelling is defined as removing a patient's reported allergy if no adverse immune-mediated reaction is noted following a direct oral provocation with the implicated drugs.

Table 4: SECONDARY OUTCOMES

Secondary outcomes

Feasibility outcome measures:

- Proportion of patients referred to the outpatient allergy clinic that are eligible for intervention (i.e randomization) as per protocol [Eligibility to screened ratio]
- Feasibility of recruitment defined as the proportion of patients consenting to participate in the study as per protocol from eligible patients [Recruitment to eligibility ratio].
- Feasibility of intervention delivery defined as the proportion of patients randomized to the intervention arm who had the intervention delivered as per protocol. [Intervention to recruitment ratio]

Safety outcome measures:

- 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
- The proportion of patients with a penicillin allergy who experience an antibiotic associated non-immune mediated adverse event
- Protocol compliance

Exploratory efficacy outcomes

- Proportion of patients with positive penicillin skin test
- Proportion of patients with non-immune mediated positive oral provocation
- Proportion of patients with severe adverse reaction – anaphylaxis/death
- Time from randomization to delabelling
- Number of appointments required for penicillin allergy delabelling
- Assessment with the Pre-Questionnaire and the 6-month follow-up Questionnaire (**Table 1 and 3**)

2.11. Statistical analysis

Results will be presented according to CONSORT guidelines. The analysis will be according to intention-to-treat, with additional per-protocol analysis. Descriptive statistics for participant characteristics,

penicillin allergy history, and why participants did not undergo an assessment will be presented. To ensure consistency all continuous variables will be presented as median (interquartile range) and categorical variables as frequency (percentage). The immediate result will be presented as the absolute difference of the primary outcome between groups with a 90% confidence interval (due to one-sided 5% significance used in sample calculation). If the upper level of this interval is greater than the non-inferiority margin (5%), the null hypothesis cannot be rejected. Feasibility outcomes will be presented as a percentage with 95% confidence intervals (CI). All other secondary outcomes will be presented as the difference in proportion with 95% CI. Continuous outcomes (time from randomization to delabelling, number of appointments, and quality of life) will be compared using negative binomial or linear regression (depending on the distribution). Missing data is expected to be minimal. If present, it will be imputed using multiple imputations separately for each treatment arm [19]. Sensitivity analysis will include complete case. No interim analysis will be performed. Subgroup analysis will be performed by including interaction term in binomial regression, results will be expressed as risk differences. Statistical analysis plan will be made available online prior to the completion of recruitment. All analysis will be conducted using StataCorp. 2019 (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

2.12. Governance

An independent data safety management board (DSMB) will review the study's progress and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. The DSMB will be comprised of a minimum of two clinicians (infectious disease or allergy immunology specialist and one statistician. 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 recommend whether the study should continue or be terminated and consider participant safety or other circumstances as grounds for early termination, including compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g., poor participant enrolment).

The DSMB will be advisory to the Trial Management Group (TMG). The TMG will be comprised by Sponsor-Investigator, the trial statistician, the trial coordinator and other important members from the coordinating site. The TMG will oversee the day-to-day conduct of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. The TMG will also be responsible for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties, such as the investigators. Each investigator will be responsible to inform their respective Institutional Review Board.

2.13. Patient and Public Involvement

No patient involved.

3. ETHICS AND DISSEMINATION

The study will be performed according to the guidelines of the Helsinki Declaration [6] and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia,

Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605).

All eligible participants will be provided with a verbal explanation of the project and written information included in the consent form. One of the study investigators will thoroughly assess the participant's competence and capacity to make a good informed decision before the participants are recruited. All participants will be deemed competent if they (1) can comprehend and retain information relevant to making the decision, (2) understand the information and implications of the decision, and (3) are able to evaluate the information and decide. For competent non-English/French speaking participants an interpreter can be used as needed.

Combining these routinely collected data and information derived from this study will provide helpful clinical insights into the management of penicillin allergy, and we plan to publish our findings. The final dataset will be the propriety of the Austin Health and contractual agreements were signed between all participating institutions and the Austin Health. The Investigational team will determine authorship concerning the International Committee of Medical Journal Editors guidelines. The results of this research project will be published and presented in various scientific forums without any identifying information about participants. The data collected from all the recruited centers mentioned above will be analyzed together and might serve for local practice change in the implicated hospitals but might also be considered part of new drug allergy guidelines. The entire protocol, the participant-level dataset, and the statistical code will be available on request after the study is completed and findings published.

Contributorship statement: JT and AC planned the study design and wrote the protocol. FJ contributed to the protocol manuscript as well as the ethics submission process. SV provided valuable information concerning the suitable statistical analysis and the study design. All authors will be responsible for collecting, managing, analyzing, and interpreting data and writing the report. All authors reviewed the protocol and this manuscript.

Competing interests: None to declare

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Data sharing statement: Technical appendix, statistical code, and dataset will available upon request.

Registration details: This trial is registered on Clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (NCT04454229).

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Figure 1: PEN-FAST CLINICAL DECISION RULE

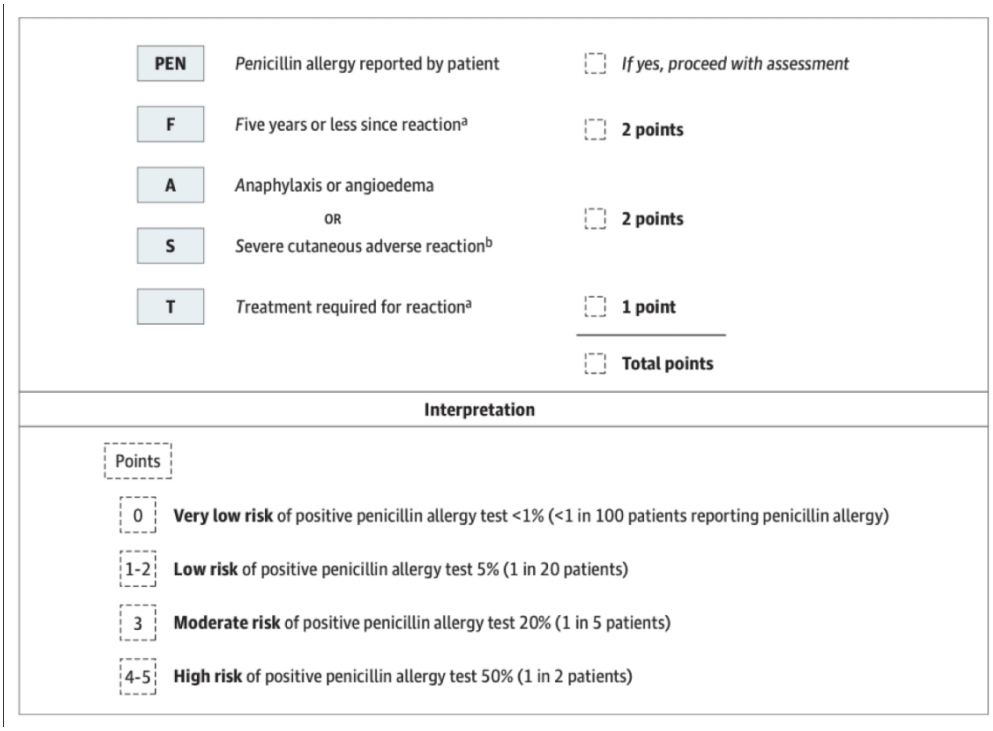
[a] Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts

[b] Includes unknown

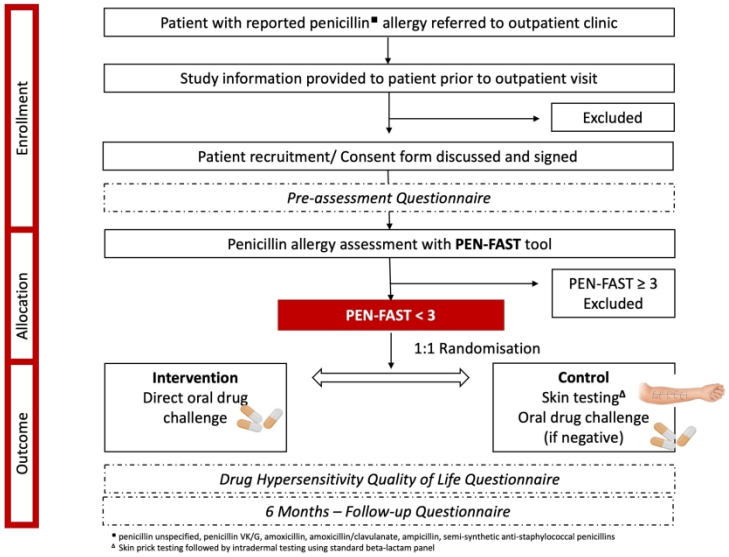
Figure 2: OVERVIEW OF THE STUDY DESIGN

▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, semi-synthetic anti-staphylococcal penicillins

Δ Skin prick testing followed by intradermal testing using standard beta-lactam panel



216x156mm (150 x 150 DPI)



338x190mm (263 x 263 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 and 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1 and 8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7prote
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study Protocol - The use of a penicillin allergy clinical decision rule to enable direct oral penicillin provocation: an international multicenter randomized control trial in an adult population (PALACE)

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Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Infectious diseases
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Study Protocol - The use of a penicillin allergy clinical decision rule to enable direct oral penicillin provocation: an international multicenter randomized control trial in an adult population (PALACE)

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11. The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Trial Registry: ClinicalTrials.gov and ANZ-CTR (NCT04454229)

Protocol version: 4

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Conflicts of interests: None to declare

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ABSTRACT

Introduction

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. More than 85% of all penicillin allergy labels can be removed by skin testing and 96-99% of low-risk penicillin allergy labels can be removed by direct oral challenge. An internally and externally validated clinical assessment tool for penicillin allergy, PEN-FAST, can identify a low-risk penicillin allergy without the need for skin testing; a score of less than 3 has a negative predictive value (NPV) of 96.3% (95% CI, 94.1-97.8) for the presence of a penicillin allergy. It is hypothesized that PEN-FAST is a safe and effective tool for assessing penicillin allergy in an outpatient clinic setting.

Methods and analysis

This is an international, multicenter randomized control trial using the PEN-FAST tool to risk-stratify penicillin allergy labels in adult outpatients. The study's primary objective is to evaluate the non-inferiority of using PEN-FAST score-guided management with direct oral challenge compared with standard care (defined as prick and intradermal skin testing followed by oral penicillin challenge). Participants will be randomized 1:1 to the intervention arm (direct oral penicillin challenge) or standard of care arm (skin testing followed by oral penicillin challenge, if skin testing is negative). The sample size of 380 randomized patients (190 per treatment arm) is required to demonstrate non-inferiority.

Ethics and dissemination

The study will be performed according to the guidelines of the Helsinki Declaration and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia, Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605). The results of this study will be published and presented in various scientific forums.

Registration details: This trial is registered on Clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (NCT04454229).

Keywords: Drug Hypersensitivity, Penicillin, Skin Tests, Drug Evaluation

Strengths and limitations of this study

- This is an international multicenter, prospective non-inferiority randomized clinical trial.
- The investigators will use a validated clinical tool, the PEN-FAST as part of the inclusion criteria in the study.
- In terms of the limitations, this study excludes the pediatric population, considering that the clinical tool PEN-FAST was validated in an adult population.
- The recruiting institutions are specialized drug allergy centers that offer skin testing as standard of care.
- Finally, the conclusions from this trial might not be generalizable beyond the enrolled study population considering that the participants that consent to participate in this trial could be different from those that decline consent.

1. INTRODUCTION

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. Patient-reported penicillin allergies and incorrect antibiotic allergy labels result in poor health outcomes for patients, including increased length of stay and mortality rate during hospitalization [1, 2], and drive inappropriate antibiotic prescribing and antimicrobial resistance, increase side effects from second-line antibiotics, and increase healthcare costs [3-7].

Work from our group has shown that more than 85% of all penicillin allergy labels can be removed by formal skin testing [8] and 96-99% of low-risk penicillin allergies can be removed by point-of-care oral challenge [9-11]. We have internally and externally validated a novel penicillin allergy clinician decision rule (PEN-FAST) that can identify low-risk penicillin allergies (**Figure 1**) [12]. In patients with a reported penicillin allergy (**PEN**), based on four allergy history criteria (time since reaction ≤5 years (**F**), anaphylaxis or angioedema (**A**), severe cutaneous adverse reaction (**S**), or whether treatment (**T**) was required for reaction), a **PEN-FAST** score of < 3 is associated with 96.7% negative predictive value [12]. A PEN-FAST score of less than 3 classified 460/622 (74%) patients as low-risk [12]. Seventeen (3.7%) of these patients had a positive penicillin allergy test. This was subsequently externally validated against a retrospective multicenter cohort of 945 outpatients from Australia and the USA with consistent results [12].

A prospective randomized controlled trial evaluating the safety of drug challenge in patients with a low-risk penicillin allergy patient group (defined as skin rash, hives, itching, or unknown reaction that occurred more than 10 years before the assessment and that did not require emergency medical attention) has been reported [13]. Specifically, the authors included 159 allergic patients in the randomization (1:1) and compared skin testing followed by drug challenge (if skin testing negative) versus a gradual 2-step direct challenge. They identified 3/79 patients (3.8%) with a positive challenge (immediate skin manifestations treated with antihistamines, no epinephrine use), showing that the challenge was a safe and effective alternative for delabelling penicillin allergy. Further, a pre-operative clinic used 3 criteria ((1) an allergy history of more than 15 years prior and either an unknown reaction, (2) a non-itchy rash or (3) a type A adverse drug reaction) to identify 119 low-risk patients from a cohort of 219 patients [14]. Among these, 55/56 (98%) patients were successfully delabelled (3 dose amoxicillin challenge 5mg/50mg/500mg at 20 min interval followed by a 3-day course of amoxicillin) with one patient developed a delayed exanthem [14]. Similar, 328 military recruits that reported penicillin or cephalosporin allergy were challenged to a single-dose direct oral challenge with amoxicillin (250 mg) [15]. Five (1.5%) demonstrated an adverse drug reaction without anaphylaxis and were treated with oral anti-histamine and intramuscular adrenaline (to prevent reaction progression) [15]. The remaining 323 participants also received an intramuscular dose of benzathine penicillin without any reported adverse reactions [15]. A prospective two-year inpatient delabelling study in an intensive care unit setting with 12-16% prevalence of penicillin allergy labels identified around 60% of penicillin allergy labeled patients as low-risk [11]. When challenged with amoxicillin, 203/205 (99%) tolerated their challenge leading to label removal, and only two cases (<1%) had rash that led to return of the allergy label after a challenge or subsequent treatment [10].

Direct drug challenges, including penicillin, have been increasingly used in the outpatient setting [16, 17]. However, no multicenter randomized control trial utilizing a validated risk assessment tool has been

undertaken to assess the safety of direct oral penicillin challenge in the outpatient setting. In our international multi-center cohort study, we will use the validated clinical tool, PEN-FAST, to determine if a direct oral penicillin challenge, where PEN-FAST score < 3, is safe and effective when compared with standard of care penicillin skin testing followed by oral penicillin challenge.

2. METHODS AND ANALYSIS

2.1. Study Design

This is an international multicenter, prospective, non-inferiority randomized clinical trial (**Figure 2**) to be conducted in the outpatient drug allergy services at Austin Health (Melbourne, Victoria, Australia), Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia), Royal Melbourne Hospital (Melbourne, Victoria, Australia), Vanderbilt University Medical Center (Nashville, Tennessee, United States), Duke University Medical Center (Durham, NC, United States), and McGill University Health Centre (Montreal, Quebec, Canada).

2.2. Eligibility criteria section

We will include adult patients (≥ 18 years) reporting a penicillin allergy label where the calculated PEN-FAST score is less than 3. Participants will be excluded if they (1) present any illness that, in the investigator's judgment, will substantially increase the risk associated with their participation in this study, including neurological or psychological conditions; (2) have a history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis; (3) report an allergy history that cannot be confirmed; or (4) are on concurrent antihistamine therapy or receiving more than stress dose steroids (i.e.,> 50mg QID hydrocortisone or steroid equivalent). Pregnant patients will also be excluded from the study.

The various ethnic backgrounds of the recruited patients will be collected and subcategorized under (1) Caucasian, (2) East Asian, (3) Indo Asian, (4) African, (5) Hispanic or Latino, (6) Aboriginal or Torres Strait Islander and (7) other. All three Australian academic centers evaluate Aboriginal or Torres Strait Islander patients and the McGill University Health Centre covers a large and varied territory, stretching from Montreal to Nunavik in the far north. Both centers in the United states evaluate Hispanic patients, with this population representing 18% of the US total population. All recruiting centers are referred adults from the age of 18 with patient from all stages of life being assessed.

Potentially eligible patients referred to the outpatient clinic reporting a penicillin allergy will be identified and assessed with a standard clinical history and calculation of the PEN-FAST score (**Figure 1**). A penicillin allergy label will be defined as patients reporting an allergy to any of the following drugs: "unspecified," penicillin VK, penicillin G, amoxicillin, amoxicillin/clavulanate, ampicillin, flucloxacillin, or dicloxacillin.

2.3. Sample size and justification

The null hypothesis is that the difference in the proportion of positive allergy investigations, including drug provocation and skin testing, is not larger than 5 % (non-inferiority margin). To achieve 80% power, assuming the event rate in the control group is 4% [18] and type 1 error probability of 5 % (one-sided), 380 patients need to be randomized (190 per group). If the control group has lower prevalence of the

outcome (2.5% or 2.0%), the power of the study will remain at least 80% if up to 4.5% of the intervention group has the outcome. Due to the randomization, intervention, and primary outcome being collected within the same visit, loss to follow-up is expected to be minimal.

2.4. Recruitment

Allergy outpatient clinics at the participating centers receive around 800 referrals per year for penicillin allergy patients. Thus, the authors estimate that recruitment will not represent an issue for this study. We estimate that the recruitment period will be six months, excluding when the outpatients are closed due to institutional COVID-19 infection prevention-related policies. The start date for this trial is January 2022 with a recruitment period of 8-12 months.

2.5. Randomization

Participants meeting eligibility criteria will be randomized to either the intervention (direct oral penicillin provocation) or standard of care arm (skin testing followed by oral penicillin provocation if negative). Permuted block design randomization will be used, stratified by the hospital site. Randomization will be non-blinded and performed using REDCap (Research Electronic Data Capture). The allocation sequence will be developed and uploaded to REDCap by a trial statistician and will remain concealed.

2.6. Treatment Arms

Prior to the intervention or standard of care procedures, participants will be asked to complete a Drug Hypersensitivity Pre-Questionnaire (**Table 1**). The goal of this questionnaire is to evaluate the quality of life of patients with drug allergy labels, specifically penicillin. Indeed, drug allergy labels can have a significant impact on health care but the patient's perspective has seldomly been assessed in the past.
A proposed clinical workflow is described in **Appendix Figure 1**.

Table 1: Pre-Questionnaire

Please answer yes, no or non-applicable (N/A) to the following questions. Mark the appropriate box with an x. Veuillez répondre non, oui ou sans objet (N/A) aux questions suivantes.	**Yes** **Oui**	**No** **Non**	**N/A**
1. Would you like the allergist's/infectious disease's physician opinion before taking medications prescribed by other specialists? Souhaitez-vous l'avis de l'allergologue / de l'infectiologue avant de prendre des médicaments prescrits par d'autres spécialistes?	☐	☐	☐
2. Do you talk to others about your allergy problem? Parlez-vous à d'autres personnes de votre problème d'allergie?	☐	☐	☐
3. Is your family aware of your problem? Votre famille est-elle au courant de votre problème?	☐	☐	☐
4. Is your partner conscious of your problem? Votre partenaire est-il au courant de votre problème?	☐	☐	☐
5. Is your family doctor aware of your drug allergy problem? Votre médecin de famille est-il au courant de votre problème d'allergie aux médicaments?	☐	☐	☐
6. Is your community pharmacist aware of your drug allergy problem? Votre pharmacien est-il au courant de votre problème d'allergie aux médicaments?	☐	☐	☐

6. Would you be happy to have penicillin again in the community after a negative test result in clinic? Accepteriez-vous de recevoir à nouveau de la pénicilline dans la communauté après un résultat de test négatif en clinique?	□	□	□

The following questions concern the influence your drug allergy has on your quality of life. Answer every question by marking the appropriate box with an x. You may choose from one of the following answers.
Les questions suivantes portent sur l'impact de votre allergie médicamenteuse sur votre qualité de vie. Répondez à chaque question en cochant la case appropriée avec un x. Vous pouvez choisir parmi l'une des réponses suivantes.

0	1	2	3	4
Not at all	**Slightly**	**Moderately**	**Very**	**Extremely**
Pas du tout	Légèrement	Modérément	Très	Extrêmement

	0	1	2	3	4
6. Do you feel different from others? Vous sentez-vous different(e) des autres?	□	□	□	□	□
7. Do you feel unluckier from others? Vous sentez-vous moins chanceux (euse) par rapport aux autres?	□	□	□	□	□
8. Is it that even a little discomfort is a problem for you? Est-ce que même un peu d'inconfort est un problème pour vous?	□	□	□	□	□
9. Is your job efficiency affected by the problem of your allergy to medications? Votre efficacité au travail est-elle affectée par le problème de votre allergie aux médicaments?	□	□	□	□	□
10. Do you feel helpless? Vous sentez-vous impuissant(e)?	□	□	□	□	□
11. Do you sleep badly? Vous dormez mal?	□	□	□	□	□
12. Do you feel embarrassed in relationships with others? Vous sentez-vous gêné(e) dans vos relations avec les autres?	□	□	□	□	□
13. Since you are unable to take medications, does every illness limit you more than other people? Puisque vous êtes incapable de prendre des médicaments, est-ce que chaque maladie vous limite plus que les autres?	□	□	□	□	□
14. Do you have difficulties concentrating? Avez-vous des difficultés à vous concentrer?	□	□	□	□	□
15. Does your allergy problem interfere with your sexual life? Votre problème d'allergie interfère-t-il avec votre vie sexuelle?	□	□	□	□	□
16. Do you feel anguished due to your problem of allergy reaction? Vous sentez-vous angoissé à cause de votre problème de réaction allergique?	□	□	□	□	□
17. Do you feel ill? Vous vous sentez malade?	□	□	□	□	□

18. Are you restricted in your nutrition from fear of substances you might be allergic to? Êtes-vous limité(e) dans votre alimentation par peur de consommer substances auxquelles vous pourriez être allergique?	□	□	□	□	□
19. Are you afraid of being administered a medication during an emergency to which you are allergic? Avez-vous peur de recevoir un médicament auquel vous êtes allergique, en cas d'urgence?	□	□	□	□	□
20. Do you feel you can't cope with your allergy problem? Pensez-vous que vous ne pouvez pas faire face à votre problème d'allergie?	□	□	□	□	□
21. For each disease, would you be confident that there is a medication that you can safely take? Pour chaque maladie, êtes-vous certain qu'il existe un médicament que vous pouvez prendre en toute sécurité?	□	□	□	□	□
22. Are you afraid you could not deal with the pain? Avez-vous peur de ne pas pouvoir supporter la douleur?	□	□	□	□	□
23. Do you feel anxious due to your problem of allergy reaction? Vous sentez-vous anxieux en raison de votre problème de réaction allergique?	□	□	□	□	□
24. Does your problem influence your relationships with other people? Votre problème influence-t-il vos relations avec les autres?	□	□	□	□	□
25. Are you in a bad mood due to your problem of allergy reaction? Êtes-vous de mauvaise humeur en raison de votre problème de réaction allergique?	□	□	□	□	□
26. Do you feel frightened due to your problem of allergy reaction? Avez-vous peur à cause de votre problème de réaction allergique	□	□	□	□	□
27. Do you worry every time you take a medication different from ones that cause your allergic reactions? Vous inquiétez-vous à chaque fois que vous prenez un médicament différent de ceux qui provoquent vos réactions allergiques?	□	□	□	□	□
28. Do you feel tired during the day because you sleep badly at night? Vous sentez-vous fatigue(e) pendant la journée parce que vous dormez mal la nuit?	□	□	□	□	□
29. Do you give up leisure activities (sport, vacations, trips) because of your problem? Avez-vous abandonné les activités de loisirs (sport, vacances, voyages) à cause de votre problème?	□	□	□	□	□
30. Does the idea of taking a medicine make you feel anxious? L'idée de prendre un médicament vous rend-il anxieux(euse)?	□	□	□	□	□

31. Are you annoyed by frequent medical controls? Êtes-vous agacé(e) par les contrôles médicaux fréquents?	□	□	□	□	□
33. Does the problem of adverse reaction to medications affect your life? Le problème des réactions indésirables aux médicaments affecte-t-il votre vie?	□	□	□	□	□
34. How likely are you to believe a negative penicillin allergy test result? Quelle est la probabilité que vous croyiez un résultat négatif au test d'allergie à la pénicilline?	□	□	□	□	□
35. How likely do you think it is that your penicillin allergy test will be negative? Selon vous, quelle est la probabilité que votre test d'allergie à la pénicilline soit négatif?	□	□	□	□	□

Intervention: Participants will receive a single dose of oral penicillin or penicillin derivatives in the intervention group after baseline vital sign assessment (i.e., temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, skin check). Nursing staff will repeat vital signs as needed after oral challenge while observing for signs of an immune mediated adverse reaction. The vital signs are also performed for all participants 60 minutes following the oral challenge. If an antibiotic-associated adverse event is noted at any stage, the standard of care treatment will be offered by the attending clinicians (e.g., epinephrine for immediate hypersensitivity reaction).

If the patient reports a reaction to either penicillin unspecified, penicillin G, penicillin V, semi-synthetic anti-staphylococcal penicillins, ampicillin, amoxicillin or amoxicillin/clavulanate, he/she will be administered either the implicated drug or amoxicillin, consistent with site local practice. The dose used for amoxicillin is 250 mg or the lowest available dose according to center availability. The implicated drug should also be administered at the lowest available dose. For the amoxicillin/clavulanate allergic patients, they will retain an allergy label to clavulanate.

Control: In the control group, routine management will include penicillin skin prick and intradermal beta-lactam inoculation adapted from previously published studies (**Table 2**) followed by oral penicillin challenge if skin testing is negative. Vital signs, observations, and management will be the same in both groups, and patients will be able to directly contact a member of the clinical team (phone or email) if any serious or antibiotic-associated adverse events (including non-immune mediated adverse events) occur in the 24 to 48 hours after oral provocation.

Table 2: DRUG ALLERGY TESTING CONCENTRATIONS

Skin Prick Testing (read at 15 minutes)
Histamine 10mg/ml
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Intradermal Testing (0.02 ml) (read at 15 minutes)
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Abbreviations: MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

Follow-up Telephone Questionnaire: A 6-month post-randomisation telephone questionnaire, based on previous publications [11], will help assess the impact of outpatient delabelling on patient perceptions of their allergy status (**Table 3**).

Table 3: Six months follow-up Questionnaire – Adapted from **[19]**

English
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 research team). You have participated in a study on Penicillin allergy, the PALACE Study, about six months ago. We are now contacting for the second part of the study to determine what antibiotics you have used after antibiotic allergy testing at our center, (*please complete with center name*). Before we proceed further, can I please confirm your full name and date of birth? Suppose you agree to continue participating in this study. In that case, 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 help you solve them, it might take longer. If we identify some issues, we might ask for your permission to contact your local doctor or (*please complete with physician name*) at the allergy service at our center that can help you solve these problems. Taking part in this interview is entirely voluntary and will not affect your future care at the (*please complete with center name*) or other hospitals.

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 remember having a test dose of penicillin in the outpatient clinic?
If No, do you agree to schedule a follow-up appointment with (*please complete with physician name)* to discuss the investigations at the outpatient clinic further?

If Yes, please tell me whether you agree with these statements:
1. "I felt safe during the test dose."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

2. "I recommend the penicillin assessment to other patients with a penicillin allergy."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

3. What was the result of your penicillin assessment in the clinic?
    a. Penicillin allergy removed
    b. Penicillin allergy confirmed
    c. I don't know

4. Did you have any late reaction to assessment after the observation period?
    a. If Yes, state reaction:
    b. What treatment was required? (e.g., General Practitioner visit, antihistamines, topical steroids, admission to hospital)

5. Have you received an antibiotic since the test?
    a. If yes, what was the name of the antibiotic?

b. If unable to recall, prompt: Was a "penicillin"?
c. If yes (i.e., penicillin received), did you have any reaction to the penicillin?

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

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

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

9. Are you still avoiding penicillin(s)?

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

If No, Congratulations. We are happy to hear this. We will further continue with some questions.

10. Do you consider yourself allergic to penicillin? Y/N

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

b. Do you have any comments about the testing, either good or bad, for us?

If the patient states that they are **still avoiding penicillin** (Q9) or they consider **themselves allergic to penicillin** (Q10) and you have assessed them to be able to participate in a qualitative interview,

then say:

"We would like to explore these issues further. This would involve another phone interview. Would you be interested in participating? What would be a good time to call you?"

End—"That is the end of the questions. Thank you very much for your time."

French

Script d'enquête téléphonique

Consentement verbal pour les patients randomisés dans l'étude.

« Bonjour, pourrais-je parler à (nom et prénom complets du patient) ? »

Bonjour, je suis _____, (nom et fonction à l'hôpital). Vous avez participé à une étude sur l'allergie à la pénicilline, l'étude PALACE, il y a environ 6 mois. Nous vous contactons maintenant pour la deuxième partie de l'étude afin de savoir quels antibiotiques vous avez utilisé suite aux tests d'allergie dans notre centre, (nommer le centre).

Avant de poursuivre, puis-je confirmer votre nom complet et votre date de naissance ?

Si vous acceptez de continuer à participer à cette étude, nous vous poserons quelques questions sur vos allergies et les antibiotiques que vous avez pris ainsi que tout problème que vous auriez rencontré avec la prise d'antibiotiques récemment. Habituellement, l'entretien dure environ 10

minutes, mais si nous identifions certains problèmes liés à vos allergies et que nous vous aidons à résoudre ces problèmes, cela peut prendre plus de temps. Si nous identifions certains problèmes, nous pouvons vous demander la permission de contacter votre médecin local ou (nommer investigateur) au département d'allergie de notre centre qui peut vous aider à résoudre ces problèmes. La participation à cet entretien est entièrement volontaire et n'affectera pas vos futurs soins dans le (nommer le centre) ou autres hôpitaux.

Si le patient n'est pas à la maison :
« Y a-t-il un moment où je pourrais rappeler pour parler avec (nom du patient) ? »

Si le patient est occupé :
« Y a-t-il un autre meilleur moment quand je pourrais vous re-contacter?

Questions pour les patients

Vous souvenez-vous d'avoir eu une dose de pénicilline à la clinique externe?
Si Non, seriez-vous d'accord à organiser une rencontre de suivi avec (nommer l'investigateur)3 pour discuter les investigations que vous avez eu à la clinique d'allergie?

Si Oui, veuillez me dire si vous êtes d'accord avec ces affirmations :
2. "Je me sentais en sécurité pendant le test."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

2. "Je recommande l'évaluation de la pénicilline à d'autres patients allergiques à la pénicilline."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

3. Quel a été le résultat de votre évaluation concernant l'allergie à la pénicilline à la clinique ?
   a. Allergie à la pénicilline supprimée
   b. Allergie à la pénicilline confirmée
   c. Je ne sais pas

4. Avez-vous présenté une réaction retardée à l'évaluation après la période d'observation?
   a. Si oui, indiquez la réaction :
   b. Quels traitements ont été nécessaire ? (e.g.., visite chez le médecin généraliste, antihistaminiques, stéroïdes topiques, admission à l'hôpital)

5. Avez-vous reçu un antibiotique depuis le test ?
   a. Si oui, quel était le nom de l'antibiotique ?

b. Si vous ne pouvez pas vous en souvenir, demandez : est-ce que c'était une « pénicilline » ?
c. Si oui (c.-à-d. pénicilline reçue), avez-vous présenté une réaction à la pénicilline ?

6. Avez-vous reçu une lettre concernant votre allergie suite à l'évaluation? O/N

7. Avez-vous l'impression d'en savoir plus sur les allergies à la pénicilline? O/N

8. Avez-vous l'impression d'en savoir plus sur vos réactions à la pénicilline ? O/N

9. Évitez-vous toujours la (les) pénicilline(s) ?
Si oui, veuillez expliquer pourquoi ? Texte libre (le chercheur classera plus tard)

10. Vous considérez-vous allergique à la pénicilline ? O/N
Si oui, la prochaine fois que vous serez hospitalisé, diriez-vous que vous êtes allergique à la pénicilline ?
Si non, félicitations. Nous sommes heureux d'entendre cela. Nous allons continuer avec quelques questions.

11. Avez-vous des commentaires sur les tests, qu'ils soient bons ou mauvais, que vous aimeriez nous transmettre? [texte libre]

Si le patient déclare qu'il évite toujours la pénicilline (9) ou qu'il se considère allergique à la pénicilline (10) et que vous l'avez évalué pour pouvoir participer à un entretien qualitatif, alors dire:

« Nous aimerions approfondir ceci. Cela impliquerait un autre entretien téléphonique. Seriez-vous intéressé à participer? Quel serait le bon moment pour vous appeler ? »

Fin— « C'est la fin des questions. Merci beaucoup pour votre temps."

2.7. Adverse Events

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.

An antibiotic-associated immune-mediated adverse event will include any immune-mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocation judged by two independent reviewers. An antibiotic-associated adverse event will include any non-immune mediated reaction (e.g., nausea, vomiting, diarrhea) within 48 hours of oral provocation judged by two independent reviewers.

2.8. Withdrawals and Stopping Criteria

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. However, participants may request their data be destroyed if not already used in analysis. No withdrawals following randomization will be replaced.

2.9. Data management

Participants' clinical details and demographics will be recorded on electronic uniform data collection forms directly on REDCap. The collected data from every institution will then be stored on an electronic database on password-protected computers. The data from all recruiting sites will be hosted by a single REDCap database at the Austin Health. The participations sites will only have access to their locally entered patient data. A study monitor will be assigned at the Austin Health that will be responsible for data entry completion, error and consistency. According to the local institutional review board regulations, all data for this study will be retained. All electronic and paper data will be destroyed by hospital policy at the time.

2.10. Outcomes

The primary outcome is the difference in the proportion of patients with a positive oral challenge or positive skin testing (defined as an immune-mediated reaction).

Secondary outcomes are listed in **Table 4** and include (1) feasibility outcomes evaluating eligibility to screened ratio, the recruitment to eligibility ratio, and the intervention to recruitment ratio; (2) safety outcomes including protocol compliance and adverse reactions (antibiotic-associated immune-mediated adverse event or severe adverse drug reaction); and (3) efficacy outcomes. The efficacy outcomes are determined by the number of patients with non-immune reactions, the number of immediate and delayed positive skin testing. Other important elements are the time from randomization to delabelling, the number of appointments required for delabelling, participant's quality of life (**Table 4**) as well as measuring the impact on delabelling six months after the procedure (**Table 4**). In this context, delabelling is defined as removing a patient's reported allergy if no adverse immune-mediated reaction is noted following a direct oral provocation with the implicated drugs.

Table 4: SECONDARY OUTCOMES

Secondary outcomes
Feasibility outcome measures: • Proportion of patients referred to the outpatient allergy clinic that are eligible for intervention (i.e randomization) as per protocol [Eligibility to screened ratio] • Feasibility of recruitment defined as the proportion of patients consenting to participate in the study as per protocol from eligible patients [Recruitment to eligibility ratio]. • Feasibility of intervention delivery defined as the proportion of patients randomized to the intervention arm who had the intervention delivered as per protocol. [Intervention to recruitment ratio]
Safety outcome measures:

- 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
- The proportion of patients with a penicillin allergy who experience an antibiotic associated non-immune mediated adverse event
- Protocol compliance

Exploratory efficacy outcomes

- Proportion of patients with positive penicillin skin test
- Proportion of patients with non-immune mediated positive oral provocation
- Proportion of patients with severe adverse reaction – anaphylaxis/death
- Time from randomization to delabelling
- Number of appointments required for penicillin allergy delabelling
- Assessment with the Pre-Questionnaire and the 6-month follow-up Questionnaire (**Table 1 and 3**)

2.11. Statistical analysis

Results will be presented according to CONSORT guidelines. The analysis will be according to intention-to-treat, with additional per-protocol analysis. Descriptive statistics for participant characteristics, penicillin allergy history, and why participants did not undergo an assessment will be presented. To ensure consistency all continuous variables will be presented as median (interquartile range) and categorical variables as frequency (percentage). The immediate result will be presented as the absolute difference of the primary outcome between groups with a 90% confidence interval (due to one-sided 5% significance used in sample calculation). If the upper level of this interval is greater than the non-inferiority margin (5%), the null hypothesis cannot be rejected. Feasibility outcomes will be presented as a percentage with 95% confidence intervals (CI). All other secondary outcomes will be presented as the difference in proportion with 95% CI. Continuous outcomes (time from randomization to delabelling, number of appointments, and quality of life) will be compared using negative binomial or linear regression (depending on the distribution). Missing data is expected to be minimal. If present, it will be imputed using multiple imputations separately for each treatment arm [20]. Sensitivity analysis will include complete case. No interim analysis will be performed. Subgroup analysis will be performed by including interaction term in binomial regression, results will be expressed as risk differences. Statistical analysis plan will be made available online prior to the completion of recruitment. All analysis will be conducted using StataCorp. 2019 (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

2.12. Governance

An independent data safety management board (DSMB) will review the study's progress and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. The DSMB will be comprised of a minimum of two clinicians (infectious disease or allergy immunology specialist and one statistician. 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 recommend whether the study should continue or be terminated and consider participant safety or other circumstances as grounds for early termination, including compelling internal

or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g., poor participant enrolment).

The DSMB will be advisory to the Trial Management Group (TMG). The TMG will be comprised by Sponsor-Investigator, the trial statistician, the trial coordinator and other important members from the coordinating site. The TMG will oversee the day-to-day conduct of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. The TMG will also be responsible for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties, such as the investigators. Each investigator will be responsible to inform their respective Institutional Review Board.

2.13. Patient and Public Involvement

No patient involved.

3. ETHICS AND DISSEMINATION

The study will be performed according to the guidelines of the Helsinki Declaration [21] and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia, Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605).

All eligible participants will be provided with a verbal explanation of the project and written information included in the consent form. One of the study investigators will thoroughly assess the participant's competence and capacity to make a good informed decision before the participants are recruited. All participants will be deemed competent if they (1) can comprehend and retain information relevant to making the decision, (2) understand the information and implications of the decision, and (3) are able to evaluate the information and decide. For competent non-English/French speaking participants an interpreter can be used as needed.

Combining these routinely collected data and information derived from this study will provide helpful clinical insights into the management of penicillin allergy, and we plan to publish our findings. The final dataset will be the propriety of the Austin Health and contractual agreements were signed between all participating institutions and the Austin Health. The Investigational team will determine authorship concerning the International Committee of Medical Journal Editors guidelines. The results of this research project will be published and presented in various scientific forums without any identifying information about participants. The data collected from all the recruited centers mentioned above will be analyzed together and might serve for local practice change in the implicated hospitals but might also be considered part of new drug allergy guidelines. The entire protocol, the participant-level dataset, and the statistical code will be available on request after the study is completed and findings published.

The ability to deliver point-of-care penicillin allergy testing for a large cohort of patients with diverse ethnic backgrounds, without skin testing, will improve patient access to testing and utilization of preferred penicillin antibiotics.

Contributorship statement: JAT and AMC planned the study design and wrote the protocol. FJ contributed to the protocol manuscript as well as the ethics submission process. SV provided valuable information concerning the suitable statistical analysis and the study design. AC, FJ, MTR, KYLC, NEH, NAT, CS, EJP and JAT will be responsible for patient recruitment and data collection. AMC, FJ, SV, EJP and JAT will analyze and interpret the clinical data as well as structure the initial draft report.
AMC, FJ, SV, MTR, KYLC, NEH, NAT, CS, EJP and JAT reviewed the protocol and this manuscript.

Competing interests: None to declare

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Data sharing statement: Technical appendix, statistical code, and dataset will available upon request.

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Figure 1: PEN-FAST CLINICAL DECISION RULE

[a] Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts

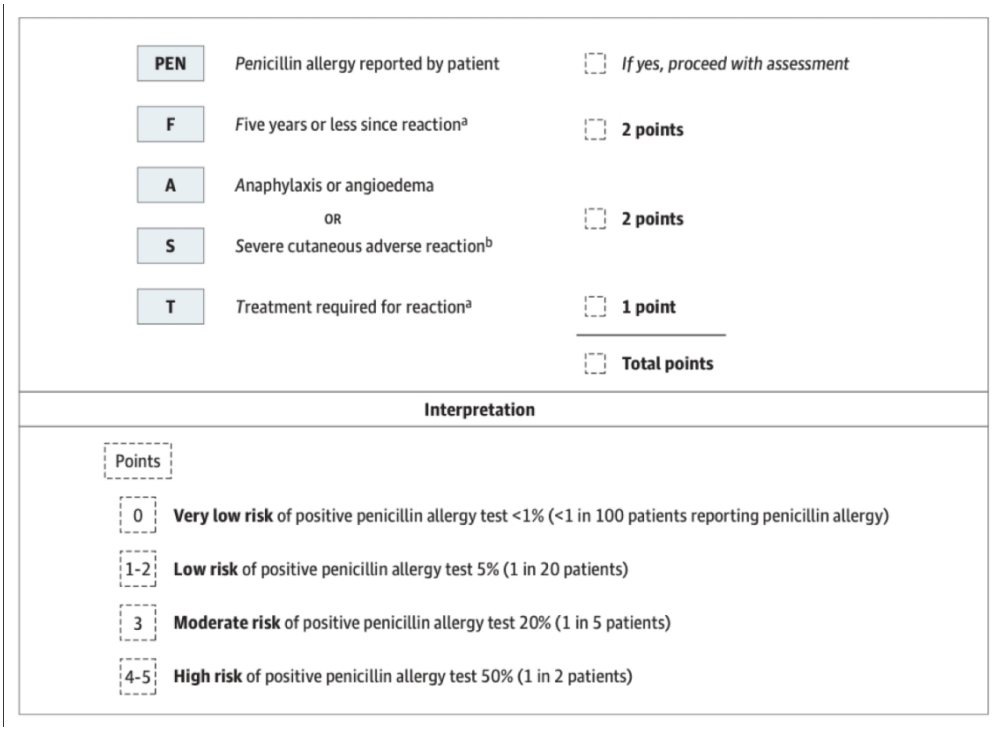
[b] Includes unknown

Figure 2: OVERVIEW OF THE STUDY DESIGN

▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, semi-synthetic anti-staphylococcal penicillins

[Δ] Skin prick testing followed by intradermal testing using standard beta-lactam panel

Appendix Figure 1: Proposed Clinical Work Flow



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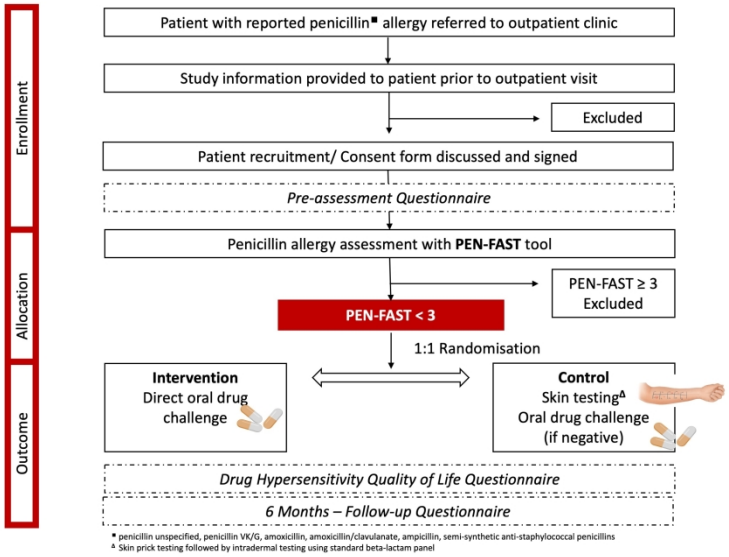


338x190mm (263 x 263 DPI)

Patient with reported penicillin▪ allergy referred to outpatient clinic

▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, dicloxacillin, flucloxacillin

Assessment for Eligibility

Inclusion Criteria

1. Adult patients (≥ 18 years) referred to the outpatient allergy clinic for a penicillin allergy history;
2. Willing and able to give consent

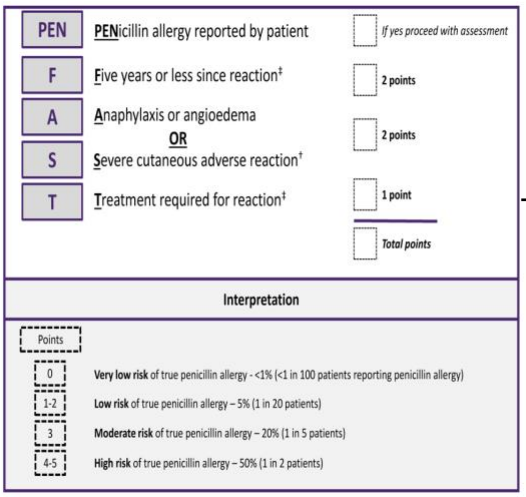
Exclusion Criteria

1. Pregnancy;
2. Any illness that, in the investigator's judgement, will substantially increase the risk associated with subject's participation in this study (**including a non-English speaking patient if an interpreter is not available**);
3. Patients with history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis;
4. Patients with a concurrent history of immune-mediated cephalosporin allergy;
5. Patients where the allergy history was not able to be confirmed with patient;
6. Patients on concurrent antihistamine therapy;
7. Patients receiving more than stress dose steroids (i.e. > 50mg QID hydrocortisone [or steroid equivalent♦]).

♦ **Approximate steroid equivalent**: Hydrocortisone 50 mg = Betamethasone 1.8 mg = Cortisone 62.5 mg = Dexamethasone 1.9 mg = Methylprednisolone 10 mg = Prednisone/Prednisolone 12.5 mg = Triamcinolone 10 mg

Patient recruitment
Consent form discussed and signed

Penicillin allergy assessment with **PEN-FAST** tool
All penicillin allergy assessment should take place during the **same medical appointment**



† 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

PEN-FAST ≥ 3
Excluded

PEN-FAST < 3

During the screening and randomization procedures, ask the patient to fill the **DRUG HYPERSENSITIVITY PRE-QUESTIONNAIRE**

1:1 Randomisation

Randomization delivered via the Research Electronic Data Capture (REDCap) software just prior to the intervention. Randomization sequence will be developed and uploaded to REDCap by a trial statistician. No other investigator or team member will have access to the sequence

Penicillin unspecified	**Penicillin VK/G OR Dicloxacillin OR Flucloxacillin**	**Amoxicillin OR Ampicillin**	**Amoxicillin/ clavulanate**
If reaction ≥ 1970			
Intervention 1 dose Amoxicillin 250 or 500 mg PO	**Intervention** 1 dose Penicillin VK 250 or 500 mg PO	**Intervention** 1 dose Amoxicillin 250 or 500 mg PO	**Intervention** 1 dose Amoxicillin 250 or 500 mg PO
Control Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention
If reaction < 1970			
Intervention 1 dose Penicillin VK 250 or 500 mg PO			
Control Skin testing If negative, challenge same as intervention			

Skin Prick Testing (read at 15 minutes)
Histamine 10mg/ml
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin 10 000 U/ml
Intradermal Testing (0.02 ml) (read at 15 minutes)
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin 10 000 U/ml

Note
Maintain clavulanate allergy label until further allergy assessment

Negative oral challenge

Remove allergy label

Positive oral challenge

An antibiotic associated immune mediated adverse event will include any immune mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocations judged by two independent reviewers.

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.

An antibiotic associated adverse event will include any non-immune mediated reaction (e.g. nausea, vomiting, diarrhea etc.) within 48 hours of oral provocations judged by two independent reviewers.

Report to Data safety management board (DSMB)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 and 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1 and 8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7prote
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Study Protocol - The use of a penicillin allergy clinical decision rule to enable direct oral penicillin provocation: an international multicenter randomized control trial in an adult population (PALACE)

Journal:	*BMJ Open*
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Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Infectious diseases
Keywords:	IMMUNOLOGY, INFECTIOUS DISEASES, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES

Study Protocol - The use of a penicillin allergy clinical decision rule to enable direct oral penicillin provocation: an international multicenter randomized control trial in an adult population (PALACE)

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11. The National Centre for Infections in Cancer, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

Trial Registry: ClinicalTrials.gov and ANZ-CTR (NCT04454229)

Protocol version: 4

Funding source: Institutional (Investigator initiated)

Conflicts of interests: None to declare

Trial Sponsor:

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ABSTRACT

Introduction

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. More than 85% of all penicillin allergy labels can be removed by skin testing and 96-99% of low-risk penicillin allergy labels can be removed by direct oral challenge. An internally and externally validated clinical assessment tool for penicillin allergy, PEN-FAST, can identify a low-risk penicillin allergy without the need for skin testing; a score of less than 3 has a negative predictive value (NPV) of 96.3% (95% CI, 94.1-97.8) for the presence of a penicillin allergy. It is hypothesized that PEN-FAST is a safe and effective tool for assessing penicillin allergy in an outpatient clinic setting.

Methods and analysis

This is an international, multicenter randomized control trial using the PEN-FAST tool to risk-stratify penicillin allergy labels in adult outpatients. The study's primary objective is to evaluate the non-inferiority of using PEN-FAST score-guided management with direct oral challenge compared with standard care (defined as prick and intradermal skin testing followed by oral penicillin challenge). Participants will be randomized 1:1 to the intervention arm (direct oral penicillin challenge) or standard of care arm (skin testing followed by oral penicillin challenge, if skin testing is negative). The sample size of 380 randomized patients (190 per treatment arm) is required to demonstrate non-inferiority.

Ethics and dissemination

The study will be performed according to the guidelines of the Helsinki Declaration and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia, Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605). The results of this study will be published and presented in various scientific forums.

Registration details: This trial is registered on Clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry (NCT04454229).

Keywords: Drug Hypersensitivity, Penicillin, Skin Tests, Drug Evaluation

Strengths and limitations of this study

- This is an international multicenter, prospective non-inferiority randomized clinical trial.
- The investigators will use a validated clinical tool, the PEN-FAST as part of the inclusion criteria in the study.
- In terms of the limitations, this study excludes the pediatric population, considering that the clinical tool PEN-FAST was validated in an adult population.
- The recruiting institutions are specialized drug allergy centers that offer skin testing as standard of care.
- Finally, the conclusions from this trial might not be generalizable beyond the enrolled study population considering that the participants that consent to participate in this trial could be different from those that decline consent.

1. INTRODUCTION

Penicillin allergies are highly prevalent in the healthcare setting and associated with the prescription of second-line inferior antibiotics. Patient-reported penicillin allergies and incorrect antibiotic allergy labels result in poor health outcomes for patients, including increased length of stay and mortality rate during hospitalization [1, 2], and drive inappropriate antibiotic prescribing and antimicrobial resistance, increase side effects from second-line antibiotics, and increase healthcare costs [3-7].

Work from our group has shown that more than 85% of all penicillin allergy labels can be removed by formal skin testing [8] and 96-99% of low-risk penicillin allergies can be removed by point-of-care oral challenge [9-11]. We have internally and externally validated a novel penicillin allergy clinician decision rule (PEN-FAST) that can identify low-risk penicillin allergies (**Figure 1**) [12]. In patients with a reported penicillin allergy (**PEN**), based on four allergy history criteria (time since reaction ≤5 years (**F**), anaphylaxis or angioedema (**A**), severe cutaneous adverse reaction (**S**), or whether treatment (**T**) was required for reaction), a **PEN-FAST** score of < 3 is associated with 96.7% negative predictive value [12]. A PEN-FAST score of less than 3 classified 460/622 (74%) patients as low-risk [12]. Seventeen (3.7%) of these patients had a positive penicillin allergy test. This was subsequently externally validated against a retrospective multicenter cohort of 945 outpatients from Australia and the USA with consistent results [12].

A prospective randomized controlled trial evaluating the safety of drug challenge in patients with a low-risk penicillin allergy patient group (defined as skin rash, hives, itching, or unknown reaction that occurred more than 10 years before the assessment and that did not require emergency medical attention) has been reported [13]. Specifically, the authors included 159 allergic patients in the randomization (1:1) and compared skin testing followed by drug challenge (if skin testing negative) versus a gradual 2-step direct challenge. They identified 3/79 patients (3.8%) with a positive challenge (immediate skin manifestations treated with antihistamines, no epinephrine use), showing that the challenge was a safe and effective alternative for delabelling penicillin allergy. Further, a pre-operative clinic used 3 criteria ((1) an allergy history of more than 15 years prior and either an unknown reaction, (2) a non-itchy rash or (3) a type A adverse drug reaction) to identify 119 low-risk patients from a cohort of 219 patients [14]. Among these, 55/56 (98%) patients were successfully delabelled (3 dose amoxicillin challenge 5mg/50mg/500mg at 20 min interval followed by a 3-day course of amoxicillin) with one patient developed a delayed exanthem [14]. Similar, 328 military recruits that reported penicillin or cephalosporin allergy were challenged to a single-dose direct oral challenge with amoxicillin (250 mg) [15]. Five (1.5%) demonstrated an adverse drug reaction without anaphylaxis and were treated with oral anti-histamine and intramuscular adrenaline (to prevent reaction progression) [15]. The remaining 323 participants also received an intramuscular dose of benzathine penicillin without any reported adverse reactions [15]. A prospective two-year inpatient delabelling study in an intensive care unit setting with 12-16% prevalence of penicillin allergy labels identified around 60% of penicillin allergy labeled patients as low-risk [11]. When challenged with amoxicillin, 203/205 (99%) tolerated their challenge leading to label removal, and only two cases (<1%) had rash that led to return of the allergy label after a challenge or subsequent treatment [10].

Direct drug challenges, including penicillin, have been increasingly used in the outpatient setting [16, 17]. However, no multicenter randomized control trial utilizing a validated risk assessment tool has been

undertaken to assess the safety of direct oral penicillin challenge in the outpatient setting. In our international multi-center cohort study, we will use the validated clinical tool, PEN-FAST, to determine if a direct oral penicillin challenge, where PEN-FAST score < 3, is safe and effective when compared with standard of care penicillin skin testing followed by oral penicillin challenge.

2. METHODS AND ANALYSIS

2.1. Study Design

This is an international multicenter, prospective, non-inferiority randomized clinical trial (**Figure 2**) to be conducted in the outpatient drug allergy services at Austin Health (Melbourne, Victoria, Australia), Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia), Royal Melbourne Hospital (Melbourne, Victoria, Australia), Vanderbilt University Medical Center (Nashville, Tennessee, United States), Duke University Medical Center (Durham, NC, United States), and McGill University Health Centre (Montreal, Quebec, Canada).

2.2. Eligibility criteria section

We will include adult patients (≥ 18 years) reporting a penicillin allergy label where the calculated PEN-FAST score is less than 3. Participants will be excluded if they (1) present any illness that, in the investigator's judgment, will substantially increase the risk associated with their participation in this study, including neurological or psychological conditions; (2) have a history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis; (3) report an allergy history that cannot be confirmed; or (4) are on concurrent antihistamine therapy or receiving more than stress dose steroids (i.e.,> 50mg QID hydrocortisone or steroid equivalent). Pregnant patients will also be excluded from the study.

The various ethnic backgrounds of the recruited patients will be collected and subcategorized under (1) Caucasian, (2) East Asian, (3) Indo Asian, (4) African, (5) Hispanic or Latino, (6) Aboriginal or Torres Strait Islander and (7) other. All three Australian academic centers evaluate Aboriginal or Torres Strait Islander patients and the McGill University Health Centre covers a large and varied territory, stretching from Montreal to Nunavik in the far north. Both centers in the United states evaluate Hispanic patients, with this population representing 18% of the US total population. All recruiting centers are referred adults from the age of 18 with patient from all stages of life being assessed.

Potentially eligible patients referred to the outpatient clinic reporting a penicillin allergy will be identified and assessed with a standard clinical history and calculation of the PEN-FAST score (**Figure 1**). A penicillin allergy label will be defined as patients reporting an allergy to any of the following drugs: "unspecified," penicillin VK, penicillin G, amoxicillin, amoxicillin/clavulanate, ampicillin, flucloxacillin, or dicloxacillin.

2.3. Sample size and justification

The null hypothesis is that the difference in the proportion of positive allergy investigations, including drug provocation and skin testing, is not larger than 5 % (non-inferiority margin). To achieve 80% power, assuming the event rate in the control group is 4% [18] and type 1 error probability of 5 % (one-sided), 380 patients need to be randomized (190 per group). If the control group has lower prevalence of the

outcome (2.5% or 2.0%), the power of the study will remain at least 80% if up to 4.5% of the intervention group has the outcome. Due to the randomization, intervention, and primary outcome being collected within the same visit, loss to follow-up is expected to be minimal.

2.4. Recruitment

Allergy outpatient clinics at the participating centers receive around 800 referrals per year for penicillin allergy patients. Thus, the authors estimate that recruitment will not represent an issue for this study. We estimate that the recruitment period will be six months, excluding when the outpatients are closed due to institutional COVID-19 infection prevention-related policies. The start date for this trial is January 2022 with a recruitment period of 8-12 months.

2.5. Randomization

Participants meeting eligibility criteria will be randomized to either the intervention (direct oral penicillin provocation) or standard of care arm (skin testing followed by oral penicillin provocation if negative). Permuted block design randomization will be used, stratified by the hospital site. Randomization will be non-blinded and performed using REDCap (Research Electronic Data Capture). The allocation sequence will be developed and uploaded to REDCap by a trial statistician and will remain concealed.

2.6. Treatment Arms

Prior to the intervention or standard of care procedures, participants will be asked to complete a Drug Hypersensitivity Pre-Questionnaire (**Table 1**). The goal of this questionnaire is to evaluate the quality of life of patients with drug allergy labels, specifically penicillin. Indeed, drug allergy labels can have a significant impact on health care but the patient's perspective has seldomly been assessed in the past.
A proposed clinical workflow is described in **Appendix Figure 1**.

Table 1: Pre-Questionnaire

Please answer yes, no or non-applicable (N/A) to the following questions. Mark the appropriate box with an x. Veuillez répondre non, oui ou sans objet (N/A) aux questions suivantes.	**Yes** **Oui**	**No** **Non**	**N/A**
1. Would you like the allergist's/infectious disease's physician opinion before taking medications prescribed by other specialists? Souhaitez-vous l'avis de l'allergologue / de l'infectiologue avant de prendre des médicaments prescrits par d'autres spécialistes?	☐	☐	☐
2. Do you talk to others about your allergy problem? Parlez-vous à d'autres personnes de votre problème d'allergie?	☐	☐	☐
3. Is your family aware of your problem? Votre famille est-elle au courant de votre problème?	☐	☐	☐
4. Is your partner conscious of your problem? Votre partenaire est-il au courant de votre problème?	☐	☐	☐
5. Is your family doctor aware of your drug allergy problem? Votre médecin de famille est-il au courant de votre problème d'allergie aux médicaments?	☐	☐	☐
6. Is your community pharmacist aware of your drug allergy problem? Votre pharmacien est-il au courant de votre problème d'allergie aux médicaments?	☐	☐	☐

6. Would you be happy to have penicillin again in the community after a negative test result in clinic? Accepteriez-vous de recevoir à nouveau de la pénicilline dans la communauté après un résultat de test négatif en clinique?	□	□	□

The following questions concern the influence your drug allergy has on your quality of life. Answer every question by marking the appropriate box with an x. You may choose from one of the following answers.
Les questions suivantes portent sur l'impact de votre allergie médicamenteuse sur votre qualité de vie. Répondez à chaque question en cochant la case appropriée avec un x. Vous pouvez choisir parmi l'une des réponses suivantes.

0	1	2	3	4
Not at all	**Slightly**	**Moderately**	**Very**	**Extremely**
Pas du tout	Légèrement	Modérément	Très	Extrêmement

	0	1	2	3	4
6. Do you feel different from others? Vous sentez-vous different(e) des autres?	□	□	□	□	□
7. Do you feel unluckier from others? Vous sentez-vous moins chanceux (euse) par rapport aux autres?	□	□	□	□	□
8. Is it that even a little discomfort is a problem for you? Est-ce que même un peu d'inconfort est un problème pour vous?	□	□	□	□	□
9. Is your job efficiency affected by the problem of your allergy to medications? Votre efficacité au travail est-elle affectée par le problème de votre allergie aux médicaments?	□	□	□	□	□
10. Do you feel helpless? Vous sentez-vous impuissant(e)?	□	□	□	□	□
11. Do you sleep badly? Vous dormez mal?	□	□	□	□	□
12. Do you feel embarrassed in relationships with others? Vous sentez-vous gêné(e) dans vos relations avec les autres?	□	□	□	□	□
13. Since you are unable to take medications, does every illness limit you more than other people? Puisque vous êtes incapable de prendre des médicaments, est-ce que chaque maladie vous limite plus que les autres?	□	□	□	□	□
14. Do you have difficulties concentrating? Avez-vous des difficultés à vous concentrer?	□	□	□	□	□
15. Does your allergy problem interfere with your sexual life? Votre problème d'allergie interfère-t-il avec votre vie sexuelle?	□	□	□	□	□
16. Do you feel anguished due to your problem of allergy reaction? Vous sentez-vous angoissé à cause de votre problème de réaction allergique?	□	□	□	□	□
17. Do you feel ill? Vous vous sentez malade?	□	□	□	□	□

18. Are you restricted in your nutrition from fear of substances you might be allergic to? Êtes-vous limité(e) dans votre alimentation par peur de consommer substances auxquelles vous pourriez être allergique?	□	□	□	□	□
19. Are you afraid of being administered a medication during an emergency to which you are allergic? Avez-vous peur de recevoir un médicament auquel vous êtes allergique, en cas d'urgence?	□	□	□	□	□
20. Do you feel you can't cope with your allergy problem? Pensez-vous que vous ne pouvez pas faire face à votre problème d'allergie?	□	□	□	□	□
21. For each disease, would you be confident that there is a medication that you can safely take? Pour chaque maladie, êtes-vous certain qu'il existe un médicament que vous pouvez prendre en toute sécurité?	□	□	□	□	□
22. Are you afraid you could not deal with the pain? Avez-vous peur de ne pas pouvoir supporter la douleur?	□	□	□	□	□
23. Do you feel anxious due to your problem of allergy reaction? Vous sentez-vous anxieux en raison de votre problème de réaction allergique?	□	□	□	□	□
24. Does your problem influence your relationships with other people? Votre problème influence-t-il vos relations avec les autres?	□	□	□	□	□
25. Are you in a bad mood due to your problem of allergy reaction? Êtes-vous de mauvaise humeur en raison de votre problème de réaction allergique?	□	□	□	□	□
26. Do you feel frightened due to your problem of allergy reaction? Avez-vous peur à cause de votre problème de réaction allergique	□	□	□	□	□
27. Do you worry every time you take a medication different from ones that cause your allergic reactions? Vous inquiétez-vous à chaque fois que vous prenez un médicament différent de ceux qui provoquent vos réactions allergiques?	□	□	□	□	□
28. Do you feel tired during the day because you sleep badly at night? Vous sentez-vous fatigue(e) pendant la journée parce que vous dormez mal la nuit?	□	□	□	□	□
29. Do you give up leisure activities (sport, vacations, trips) because of your problem? Avez-vous abandonné les activités de loisirs (sport, vacances, voyages) à cause de votre problème?	□	□	□	□	□
30. Does the idea of taking a medicine make you feel anxious? L'idée de prendre un médicament vous rend-il anxieux(euse)?	□	□	□	□	□

31. Are you annoyed by frequent medical controls? Êtes-vous agacé(e) par les contrôles médicaux fréquents?	□	□	□	□	□
33. Does the problem of adverse reaction to medications affect your life? Le problème des réactions indésirables aux médicaments affecte-t-il votre vie?	□	□	□	□	□
34. How likely are you to believe a negative penicillin allergy test result? Quelle est la probabilité que vous croyiez un résultat négatif au test d'allergie à la pénicilline?	□	□	□	□	□
35. How likely do you think it is that your penicillin allergy test will be negative? Selon vous, quelle est la probabilité que votre test d'allergie à la pénicilline soit négatif?	□	□	□	□	□

Intervention: Participants will receive a single dose of oral penicillin or penicillin derivatives in the intervention group after baseline vital sign assessment (i.e., temperature, heart rate, blood pressure, respiratory rate, oxygen saturation, skin check). Nursing staff will repeat vital signs as needed after oral challenge while observing for signs of an immune mediated adverse reaction. The vital signs are also performed for all participants 60 minutes following the oral challenge. If an antibiotic-associated adverse event is noted at any stage, the standard of care treatment will be offered by the attending clinicians (e.g., epinephrine for immediate hypersensitivity reaction).

If the patient reports a reaction to either penicillin unspecified, penicillin G, penicillin V, semi-synthetic anti-staphylococcal penicillins, ampicillin, amoxicillin or amoxicillin/clavulanate, he/she will be administered either the implicated drug or amoxicillin, consistent with site local practice. The dose used for amoxicillin is 250 mg or the lowest available dose according to center availability. The implicated drug should also be administered at the lowest available dose. For the amoxicillin/clavulanate allergic patients, they will retain an allergy label to clavulanate.

Control: In the control group, routine management will include penicillin skin prick and intradermal beta-lactam inoculation adapted from previously published studies (**Table 2**) followed by oral penicillin challenge if skin testing is negative. Vital signs, observations, and management will be the same in both groups, and patients will be able to directly contact a member of the clinical team (phone or email) if any serious or antibiotic-associated adverse events (including non-immune mediated adverse events) occur in the 24 to 48 hours after oral provocation.

Table 2: DRUG ALLERGY TESTING CONCENTRATIONS

Skin Prick Testing (read at 15 minutes)
Histamine 10mg/ml
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Intradermal Testing (0.02 ml) (read at 15 minutes)
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin G 10 000 U/ml

Abbreviations: MDM, minor determinant mixture; PPL, penicilloyl-polylysine.

Follow-up Telephone Questionnaire: A 6-month post-randomisation telephone questionnaire, based on previous publications [11], will help assess the impact of outpatient delabelling on patient perceptions of their allergy status (**Table 3**).

Table 3: Six months follow-up Questionnaire – Adapted from **[19]**

English
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 research team). You have participated in a study on Penicillin allergy, the PALACE Study, about six months ago. We are now contacting for the second part of the study to determine what antibiotics you have used after antibiotic allergy testing at our center, (*please complete with center name*). Before we proceed further, can I please confirm your full name and date of birth? Suppose you agree to continue participating in this study. In that case, 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 help you solve them, it might take longer. If we identify some issues, we might ask for your permission to contact your local doctor or (*please complete with physician name*) at the allergy service at our center that can help you solve these problems. Taking part in this interview is entirely voluntary and will not affect your future care at the (*please complete with center name*) or other hospitals.

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 remember having a test dose of penicillin in the outpatient clinic?
If No, do you agree to schedule a follow-up appointment with (*please complete with physician name)* to discuss the investigations at the outpatient clinic further?

If Yes, please tell me whether you agree with these statements:
1. "I felt safe during the test dose."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

2. "I recommend the penicillin assessment to other patients with a penicillin allergy."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

3. What was the result of your penicillin assessment in the clinic?
    a. Penicillin allergy removed
    b. Penicillin allergy confirmed
    c. I don't know

4. Did you have any late reaction to assessment after the observation period?
    a. If Yes, state reaction:
    b. What treatment was required? (e.g., General Practitioner visit, antihistamines, topical steroids, admission to hospital)

5. Have you received an antibiotic since the test?
    a. If yes, what was the name of the antibiotic?

b. If unable to recall, prompt: Was a "penicillin"?
c. If yes (i.e., penicillin received), did you have any reaction to the penicillin?

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

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

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

9. Are you still avoiding penicillin(s)?

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

If No, Congratulations. We are happy to hear this. We will further continue with some questions.

10. Do you consider yourself allergic to penicillin? Y/N

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

b. Do you have any comments about the testing, either good or bad, for us?

If the patient states that they are **still avoiding penicillin** (Q9) or they consider **themselves allergic to penicillin** (Q10) and you have assessed them to be able to participate in a qualitative interview,

then say:

"We would like to explore these issues further. This would involve another phone interview. Would you be interested in participating? What would be a good time to call you?"

End—"That is the end of the questions. Thank you very much for your time."

French

Script d'enquête téléphonique

Consentement verbal pour les patients randomisés dans l'étude.

« Bonjour, pourrais-je parler à (nom et prénom complets du patient) ? »

Bonjour, je suis _____, (nom et fonction à l'hôpital). Vous avez participé à une étude sur l'allergie à la pénicilline, l'étude PALACE, il y a environ 6 mois. Nous vous contactons maintenant pour la deuxième partie de l'étude afin de savoir quels antibiotiques vous avez utilisé suite aux tests d'allergie dans notre centre, (nommer le centre).

Avant de poursuivre, puis-je confirmer votre nom complet et votre date de naissance ?

Si vous acceptez de continuer à participer à cette étude, nous vous poserons quelques questions sur vos allergies et les antibiotiques que vous avez pris ainsi que tout problème que vous auriez rencontré avec la prise d'antibiotiques récemment. Habituellement, l'entretien dure environ 10

minutes, mais si nous identifions certains problèmes liés à vos allergies et que nous vous aidons à résoudre ces problèmes, cela peut prendre plus de temps. Si nous identifions certains problèmes, nous pouvons vous demander la permission de contacter votre médecin local ou (nommer investigateur) au département d'allergie de notre centre qui peut vous aider à résoudre ces problèmes. La participation à cet entretien est entièrement volontaire et n'affectera pas vos futurs soins dans le (nommer le centre) ou autres hôpitaux.

Si le patient n'est pas à la maison :
« Y a-t-il un moment où je pourrais rappeler pour parler avec (nom du patient) ? »

Si le patient est occupé :
« Y a-t-il un autre meilleur moment quand je pourrais vous re-contacter?

Questions pour les patients

Vous souvenez-vous d'avoir eu une dose de pénicilline à la clinique externe?
Si Non, seriez-vous d'accord à organiser une rencontre de suivi avec (nommer l'investigateur)3 pour discuter les investigations que vous avez eu à la clinique d'allergie?

Si Oui, veuillez me dire si vous êtes d'accord avec ces affirmations :
2. "Je me sentais en sécurité pendant le test."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

2. "Je recommande l'évaluation de la pénicilline à d'autres patients allergiques à la pénicilline."
   a. Tout à fait d'accord
   b. D'accord
   c. Neutre
   d. Pas d'accord
   e. Fortement en désaccord

3. Quel a été le résultat de votre évaluation concernant l'allergie à la pénicilline à la clinique ?
   a. Allergie à la pénicilline supprimée
   b. Allergie à la pénicilline confirmée
   c. Je ne sais pas

4. Avez-vous présenté une réaction retardée à l'évaluation après la période d'observation?
   a. Si oui, indiquez la réaction :
   b. Quels traitements ont été nécessaire ? (e.g.., visite chez le médecin généraliste, antihistaminiques, stéroïdes topiques, admission à l'hôpital)

5. Avez-vous reçu un antibiotique depuis le test ?
   a. Si oui, quel était le nom de l'antibiotique ?

b. Si vous ne pouvez pas vous en souvenir, demandez : est-ce que c'était une « pénicilline » ?
c. Si oui (c.-à-d. pénicilline reçue), avez-vous présenté une réaction à la pénicilline ?

6. Avez-vous reçu une lettre concernant votre allergie suite à l'évaluation? O/N

7. Avez-vous l'impression d'en savoir plus sur les allergies à la pénicilline? O/N

8. Avez-vous l'impression d'en savoir plus sur vos réactions à la pénicilline ? O/N

9. Évitez-vous toujours la (les) pénicilline(s) ?
Si oui, veuillez expliquer pourquoi ? Texte libre (le chercheur classera plus tard)

10. Vous considérez-vous allergique à la pénicilline ? O/N
Si oui, la prochaine fois que vous serez hospitalisé, diriez-vous que vous êtes allergique à la pénicilline ?
Si non, félicitations. Nous sommes heureux d'entendre cela. Nous allons continuer avec quelques questions.

11. Avez-vous des commentaires sur les tests, qu'ils soient bons ou mauvais, que vous aimeriez nous transmettre? [texte libre]

Si le patient déclare qu'il évite toujours la pénicilline (9) ou qu'il se considère allergique à la pénicilline (10) et que vous l'avez évalué pour pouvoir participer à un entretien qualitatif, alors dire:

« Nous aimerions approfondir ceci. Cela impliquerait un autre entretien téléphonique. Seriez-vous intéressé à participer? Quel serait le bon moment pour vous appeler ? »

Fin— « C'est la fin des questions. Merci beaucoup pour votre temps."

2.7. Adverse Events

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.

An antibiotic-associated immune-mediated adverse event will include any immune-mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocation judged by two independent reviewers. An antibiotic-associated adverse event will include any non-immune mediated reaction (e.g., nausea, vomiting, diarrhea) within 48 hours of oral provocation judged by two independent reviewers.

2.8. Withdrawals and Stopping Criteria

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. However, participants may request their data be destroyed if not already used in analysis. No withdrawals following randomization will be replaced.

2.9. Data management

Participants' clinical details and demographics will be recorded on electronic uniform data collection forms directly on REDCap. The collected data from every institution will then be stored on an electronic database on password-protected computers. The data from all recruiting sites will be hosted by a single REDCap database at the Austin Health. The participations sites will only have access to their locally entered patient data. A study monitor will be assigned at the Austin Health that will be responsible for data entry completion, error and consistency. According to the local institutional review board regulations, all data for this study will be retained. All electronic and paper data will be destroyed by hospital policy at the time.

2.10. Outcomes

The primary outcome is the difference in the proportion of positive oral challenges (i.e. immune-mediated reaction).

Secondary outcomes are listed in **Table 4** and include (1) feasibility outcomes evaluating eligibility to screened ratio, the recruitment to eligibility ratio, and the intervention to recruitment ratio; (2) safety outcomes including protocol compliance and adverse reactions (antibiotic-associated immune-mediated adverse event or severe adverse drug reaction); and (3) exploratory efficacy outcomes. The exploratory efficacy outcomes are determined by the number of patients with non-immune reactions, the number of immediate and delayed positive skin testing. Other important elements are the time from randomization to delabelling, the number of appointments required for delabelling, participant's quality of life (**Table 4**) as well as measuring the impact on delabelling six months after the procedure (**Table 4**). In this context, delabelling is defined as removing a patient's reported allergy if no adverse immune-mediated reaction is noted following a direct oral provocation with the implicated drugs.

Table 4: SECONDARY OUTCOMES

Secondary outcomes
Feasibility outcome measures: • Proportion of patients referred to the outpatient allergy clinic that are eligible for intervention (i.e randomization) as per protocol [Eligibility to screened ratio] • Feasibility of recruitment defined as the proportion of patients consenting to participate in the study as per protocol from eligible patients [Recruitment to eligibility ratio]. • Feasibility of intervention delivery defined as the proportion of patients randomized to the intervention arm who had the intervention delivered as per protocol. [Intervention to recruitment ratio]
Safety outcome measures:

- 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
- The proportion of patients with a penicillin allergy who experience an antibiotic associated non-immune mediated adverse event
- The proportion of patients that will respect the protocol (protocol compliance)

Exploratory efficacy outcomes

- Proportion of patients with positive penicillin skin test
- Proportion of patients with non-immune mediated positive oral provocation
- Proportion of patients with severe adverse reaction – anaphylaxis/death
- Time from randomization to delabelling
- Number of appointments required for penicillin allergy delabelling
- Assessment with the Pre-Questionnaire and the 6-month follow-up Questionnaire (**Table 1 and 3**)

2.11. Statistical analysis

Results will be presented according to CONSORT guidelines. The analysis will be according to intention-to-treat, with additional per-protocol analysis. Descriptive statistics for participant characteristics, penicillin allergy history, and why participants did not undergo an assessment will be presented. To ensure consistency all continuous variables will be presented as median (interquartile range) and categorical variables as frequency (percentage). The immediate result will be presented as the absolute difference of the primary outcome between groups with a 90% confidence interval (due to one-sided 5% significance used in sample calculation). If the upper level of this interval is greater than the non-inferiority margin (5%), the null hypothesis cannot be rejected. Feasibility outcomes will be presented as a percentage with 95% confidence intervals (CI). All other secondary outcomes will be presented as the difference in proportion with 95% CI. Continuous outcomes (time from randomization to delabelling, number of appointments, and quality of life) will be compared using negative binomial or linear regression (depending on the distribution). Missing data is expected to be minimal. If present, it will be imputed using multiple imputations separately for each treatment arm [20]. Sensitivity analysis will include complete case. No interim analysis will be performed. Subgroup analysis will be performed by including interaction term in binomial regression, results will be expressed as risk differences. Statistical analysis plan will be made available online prior to the completion of recruitment. All analysis will be conducted using StataCorp. 2019 (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

2.12. Governance

An independent data safety management board (DSMB) will review the study's progress and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. The DSMB will be comprised of a minimum of two clinicians (infectious disease or allergy immunology specialist and one statistician. 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 recommend whether the study should continue or be terminated and consider participant safety or other circumstances as grounds for early termination, including compelling internal

or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g., poor participant enrolment).

The DSMB will be advisory to the Trial Management Group (TMG). The TMG will be comprised by Sponsor-Investigator, the trial statistician, the trial coordinator and other important members from the coordinating site. The TMG will oversee the day-to-day conduct of a clinical trial, including safety oversight activities and/or acting on advice from other individual(s) or group(s) providing safety oversight. The TMG will also be responsible for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties, such as the investigators. Each investigator will be responsible to inform their respective Institutional Review Board.

2.13. Patient and Public Involvement

No patient involved.

3. ETHICS AND DISSEMINATION

The study will be performed according to the guidelines of the Helsinki Declaration [21] and is approved by the Austin Health Human Research Ethics Committee (HREC/62425/Austin-2020) in Melbourne Australia, Vanderbilt University Institutional Review Board (IRB #202174) in Tennessee, USA, Duke University Institutional Review Board (IRB #Pro00108461) in North Carolina, USA and McGill University Health Centre Research Ethics Board in Canada (PALACE / 2022-7605).

All eligible participants will be provided with a verbal explanation of the project and written information included in the consent form. One of the study investigators will thoroughly assess the participant's competence and capacity to make a good informed decision before the participants are recruited. All participants will be deemed competent if they (1) can comprehend and retain information relevant to making the decision, (2) understand the information and implications of the decision, and (3) are able to evaluate the information and decide. For competent non-English/French speaking participants an interpreter can be used as needed.

Combining these routinely collected data and information derived from this study will provide helpful clinical insights into the management of penicillin allergy, and we plan to publish our findings. The final dataset will be the propriety of the Austin Health and contractual agreements were signed between all participating institutions and the Austin Health. The Investigational team will determine authorship concerning the International Committee of Medical Journal Editors guidelines. The results of this research project will be published and presented in various scientific forums without any identifying information about participants. The data collected from all the recruited centers mentioned above will be analyzed together and might serve for local practice change in the implicated hospitals but might also be considered part of new drug allergy guidelines. The entire protocol, the participant-level dataset, and the statistical code will be available on request after the study is completed and findings published.

The ability to deliver point-of-care penicillin allergy testing for a large cohort of patients with diverse ethnic backgrounds, without skin testing, will improve patient access to testing and utilization of preferred penicillin antibiotics.

Contributorship statement: JAT and AMC planned the study design and wrote the protocol. FJ contributed to the protocol manuscript as well as the ethics submission process. SV provided valuable information concerning the suitable statistical analysis and the study design. AC, FJ, MTR, KYLC, NEH, NAT, CS, EJP and JAT will be responsible for patient recruitment and data collection. AMC, FJ, SV, EJP and JAT will analyze and interpret the clinical data as well as structure the initial draft report.
AMC, FJ, SV, MTR, KYLC, NEH, NAT, CS, EJP and JAT reviewed the protocol and this manuscript.

Competing interests: None to declare

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Data sharing statement: Technical appendix, statistical code, and dataset will available upon request.

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Figure 1: PEN-FAST CLINICAL DECISION RULE

[a] Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts

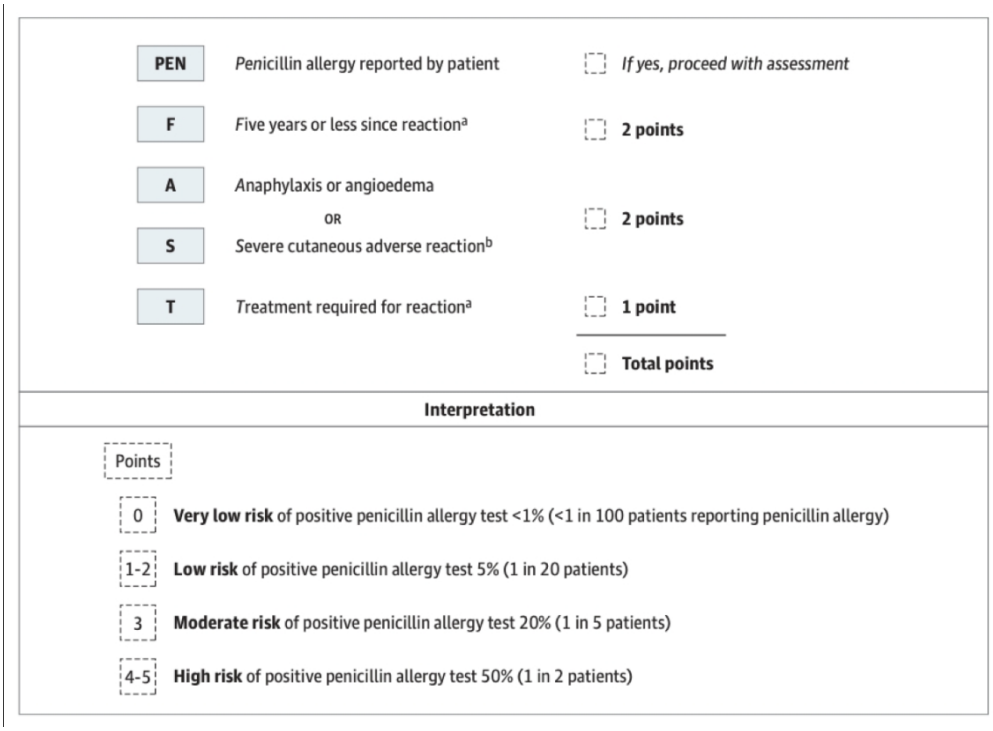
[b] Includes unknown

Figure 2: OVERVIEW OF THE STUDY DESIGN

▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, semi-synthetic anti-staphylococcal penicillins

[Δ] Skin prick testing followed by intradermal testing using standard beta-lactam panel

Appendix Figure 1: Proposed Clinical Work Flow



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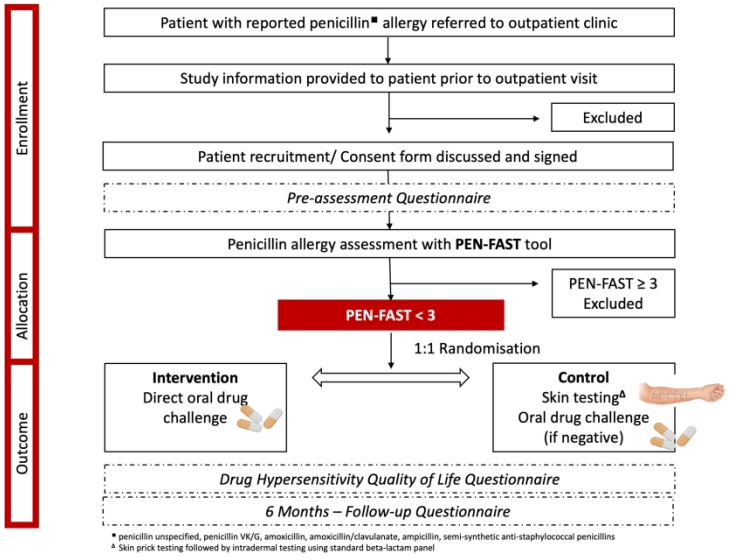


338x190mm (263 x 263 DPI)

Patient with reported penicillin▪ allergy referred to outpatient clinic

▪ penicillin unspecified, penicillin VK/G, amoxicillin, amoxicillin/clavulanate, ampicillin, dicloxacillin, flucloxacillin

Assessment for Eligibility

Inclusion Criteria

1. Adult patients (≥ 18 years) referred to the outpatient allergy clinic for a penicillin allergy history;
2. Willing and able to give consent

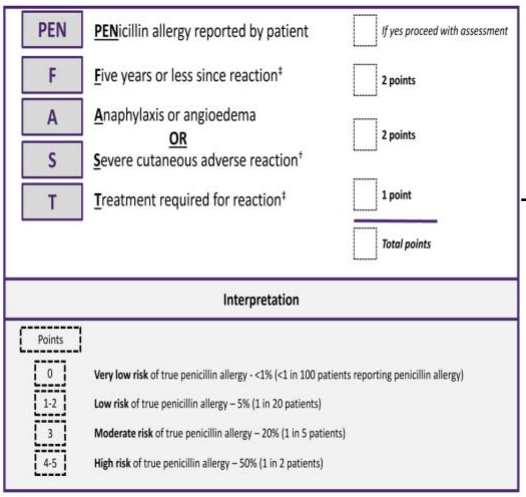
Exclusion Criteria

1. Pregnancy;
2. Any illness that, in the investigator's judgement, will substantially increase the risk associated with subject's participation in this study (**including a non-English speaking patient if an interpreter is not available**);
3. Patients with history of type A adverse drug reaction, drug-associated anaphylaxis, idiopathic urticaria/anaphylaxis, mastocytosis, serum sickness, blistering skin eruption or acute interstitial nephritis;
4. Patients with a concurrent history of immune-mediated cephalosporin allergy;
5. Patients where the allergy history was not able to be confirmed with patient;
6. Patients on concurrent antihistamine therapy;
7. Patients receiving more than stress dose steroids (i.e. > 50mg QID hydrocortisone [or steroid equivalent♦]).

♦ **Approximate steroid equivalent**: Hydrocortisone 50 mg = Betamethasone 1.8 mg = Cortisone 62.5 mg = Dexamethasone 1.9 mg = Methylprednisolone 10 mg = Prednisone/Prednisolone 12.5 mg = Triamcinolone 10 mg

Patient recruitment
Consent form discussed and signed

Penicillin allergy assessment with **PEN-FAST** tool
All penicillin allergy assessment should take place during the **same medical appointment**



† 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

PEN-FAST ≥ 3
Excluded

PEN-FAST < 3

During the screening and randomization procedures, ask the patient to fill the **DRUG HYPERSENSITIVITY PRE-QUESTIONNAIRE**

1:1 Randomisation

Randomization delivered via the Research Electronic Data Capture (REDCap) software just prior to the intervention. Randomization sequence will be developed and uploaded to REDCap by a trial statistician. No other investigator or team member will have access to the sequence

Penicillin unspecified	**Penicillin VK/G OR Dicloxacillin OR Flucloxacillin**	**Amoxicillin OR Ampicillin**	**Amoxicillin/ clavulanate**
If reaction ≥ 1970			
Intervention 1 dose Amoxicillin 250 or 500 mg PO	**Intervention** 1 dose Penicillin VK 250 or 500 mg PO	**Intervention** 1 dose Amoxicillin 250 or 500 mg PO	**Intervention** 1 dose Amoxicillin 250 or 500 mg PO
Control Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention	**Control** Skin testing If negative, challenge same as intervention
If reaction < 1970			
Intervention 1 dose Penicillin VK 250 or 500 mg PO			
Control Skin testing If negative, challenge same as intervention			

Skin Prick Testing (read at 15 minutes)
Histamine 10mg/ml
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin 10 000 U/ml
Intradermal Testing (0.02 ml) (read at 15 minutes)
Sodium Chloride 0.9%
Diater PPL (major determinant)
Diater MDM (minor determinant) (if available)
Ampicillin 25mg/ml
Penicillin 10 000 U/ml

Note
Maintain clavulanate allergy label until further allergy assessment

Negative oral challenge

Remove allergy label

Positive oral challenge

An antibiotic associated immune mediated adverse event will include any immune mediated [immediate (IgE) or non-immediate (T-cell)] reaction within 48 hours of oral provocations judged by two independent reviewers.

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.

An antibiotic associated adverse event will include any non-immune mediated reaction (e.g. nausea, vomiting, diarrhea etc.) within 48 hours of oral provocations judged by two independent reviewers.

Report to Data safety management board (DSMB)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 and 8
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1 and 8
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	8
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	n/a
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	6
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7prote
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	8
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	8
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	8
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	8
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	8
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a