PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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)
AUTHORS	Copaescu, Ana-Maria; James, Fiona; Vogrin, Sara; Rose, Morgan; Chua, Kyra; Holmes, NE; Turner, Nicholas A.; Stone, Cosby; Phillips, Elizabeth; Trubiano, Jason

VERSION 1 – REVIEW

REVIEWER	Elkhalifa, Shuayb The University of Mancheste
REVIEW RETURNED	10-May-2022

GENERAL COMMENTS	PEN-FAST is a validated clinical assessment tool for penicillin allergy risk stratification. The authors hypothesized that PEN-FAST is a safe and effective tool for assessing penicillin allergy in outpatient clinics. They have written a well-structured study protocol for this international, multicentre randomized control trial using the PEN-FAST tool to risk-stratify penicillin allergy labels in adult outpatients. There are many studies that are currently being conducted to validate such approach of safe penicillin allergy de-labelling using validated assessment tools. Few points need to be addressed to improve the manuscript: - Please indicate that this protocol is for adults in the title. - The methods will be strengthened by better understanding the demographics and characteristics of cohorts at various recruitment centres. Please comment on overall ethnicity and age breakdown at various recruitment centres, and the impact of this upon results - Elaborate further regarding the rationale for using the lengthy (35 item) pre-questionnaires. As most of the questions are not related to Penicillin allergy. - The planned study subjects of 190 seems relatively small compared to the number of the referrals in each centre. Please elaborate further? - The manuscript would be further strengthened by adding a proposed clinical workflow. Since a major goal here is the development of an outpatient-based approach of penicillin allergy de-labelling. It will help the reader (non-allergist) to better understand how patients would be manged applying the proposed protocol. - Please also indicate how this can be incorporated into the EHR system as most hospitals now using electronic health records. - Do the authors intend to recruit more centres? It would help the Journal assess generalizability of this tool if that is made clear. - Elaborate further regarding the generalisability of the results to other centres and countries.

REVIEWER	Taylor, Margaret Baylor College of Medicine, Department of Obstetrics & Gynecology
REVIEW RETURNED	11-May-2022

GENERAL COMMENTS	I read with great interest the study protocol for the multicenter randomized control PALACE trial. The use of the PEN-FAST tool is well-supported in prior reports, and the hypothesis, study design, and statistical planning are expertly outlined. I look forward to reading the results of the study, which should have important implications for antimicrobial stewardship programs across the country. I have two minor questions: 1. Question 22 on Table 1, pre-questionnaire seems vague. 2. Is there any specific plan to ensure that asthma, allergic rhinitis, COPD, or other chronic medical conditions are well-controlled prior to challenges (or is this included in exclusion criteria #4 listed in the protocol)?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1:
Thank you very much for taking the time to carefully review our article.
Comments
Comment 1: *Please indicate that this protocol is for adults in the title.*
Reply 1: Thank you very much for your comment. We have now added this to the title.
Comment 2: *The methods will be strengthened by better understanding the demographics and characteristics of cohorts at various recruitment centres. Please comment on overall ethnicity and age breakdown at various recruitment centres, and the impact of this upon results.*
Reply 2: Thank you very much. In the METHODS AND ANALYSIS section, under Eligibility criteria section, we have now added important elements regarding the demographic and ethnicity in the recruiting centers.
Comment 3: *Elaborate further regarding the rationale for using the lengthy (35 item) pre-questionnaires. As most of the questions are not related to Penicillin allergy.*
Reply 3: Thank you very much for this interesting comment. The quality of life for patients with drug allergy labels is not well understood. With this questionnaire, we wanted to be able to evaluate this in our population. We have now clarified this in section 2.6. Treatment Arms.
Comment 4: *The planned study subjects of 190 seems relatively small compared to the number of the referrals in each centre. Please elaborate further?*
Reply 4: Thank you very much for this important comment. The sample size was determined based on expected primary outcome and is 380 patients (190 per arm). While this study could be completed within a single centre, we have decided for multicentre study to aid the generalizability of the results as well as to complete the study in timely manner (especially due to impact of COVID-19 pandemic on research activities).
Comment 5: *The manuscript would be further strengthened by adding a proposed clinical workflow. Since a major goal here is the development of an outpatient-based approach of penicillin allergy de-labelling. It will help the reader (non-allergist) to better understand how patients would be manged applying the proposed protocol.*
Reply 5: Thank you very much. We have now added an appendix for the proposed clinical work flow. We have also included elements from the clinical work flow in the Study design figure.

Comment 6: *Please also indicate how this can be incorporated into the EHR system as most hospitals now using electronic health records.*
Reply 6: Thank you very much. Following penicillin allergy investigations, the allergy label will be removed from the EHR system as to allow the patient to receive the most appropriate antibiotic in the future. All the recruiting centres have an integrated EHR system.
Comment 7: *Do the authors intend to recruit more centres? It would help the Journal assess generalizability of this tool if that is made clear.*
Reply 7: We understand that the results from this study could have an impact on the assessment of low risk penicillin allergies. The goal of this randomized control trial is to determine the safety and efficacy of the direct oral challenge, compared with standard of care penicillin skin testing followed by oral penicillin challenge. In this context, with the current sample size and the implicated centres, we aim to achieve this goal. Please note that we are currently recruiting patients from 5 centres, in 3 different countries and 2 continents. Thank you.
Comment 8: *Elaborate further regarding the generalisability of the results to other centres and countries.*
Reply 8: Thank you. We have added a paragraph in the 3. ETHICS AND DISSEMINATION section.

Response to Reviewer #2:
Thank you very much for taking the time to carefully review our article.
Major comments
Comment 1: *Question 22 on Table 1, pre-questionnaire seems vague.*
Reply 1: Thank you very much. We have now clarified the goal of the pre-questionnaire in section 2.6. Treatment Arms.
"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."
Comment 2: *Is there any specific plan to ensure that asthma, allergic rhinitis, COPD, or other chronic medical conditions are well-controlled prior to challenges (or is this included in exclusion criteria #4 listed in the protocol)?*
Reply 2: Thank you for your interesting comment. As you indicated, the absence of adequate control of these conditions is a contra-indication to an oral challenge, as per standard of care. This is described in the exclusion criteria: (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.

Editor(s)' Comments to Author:
Comment 1: *Please include the trial registration details after the abstract.*
Reply 1: We have now included this. Thank you.
Comment 2: *Please ensure that your protocol reports all outcome measures for your trial and ensure that the primary and secondary outcome measures are consistent between your protocol article and the trial registry.*
Reply 2: Thank you very much for this important comment. We have now verified the information as you suggested and made the necessary changes.
Comment 3: *Please include the planned start and end dates for the study in the methods section.*
Reply 3: Thank you. This was included.
Comment 4: *In the title, please state that your manuscript is a study protocol.*
Reply 4: Thank you. This has been adjusted.

Comment 5: *Please add a reference to support the assumption of a 4% event rate in the control group (in the 'Sample size and justification' section).*
Reply 4: Thank you. The reference and further sample size scenario was added.

VERSION 2 – REVIEW

REVIEWER	Elkhalifa, Shuayb The University of Manchester
REVIEW RETURNED	19-Jun-2022

GENERAL COMMENTS	All previous comments were addressed. No further editing is required.