PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance (ALABAMA): protocol for a multicentre, parallel-arm, open label, randomised pragmatic trial
AUTHORS	Armitage, Kelsey; Porter, Catherine; Ahmed, S.; Cook, Johanna; Boards, J.; Bongard, Emily; Butler, Christopher C.; Corfield, K.; Davoudianfar, Mina; Galal, Ushma; Howard, P; Mujica-Mota, Ruben; Saman, Razan; Santillo, Marta; Savic, Sinisa; Shinkins, Bethany; Tonkin-Crine, Sarah; Wanat, Marta; West, Robert; Yu, Ly-Mee; Pavitt, Sue; Sandoe, Jonathan

VERSION 1 – REVIEW

REVIEWER	Wurcel, Alysse G Tufts University School of Medicine
REVIEW RETURNED	22-Mar-2023

GENERAL COMMENTS	Thank you for letting me review this protocol paper. It is very interesting idea and definitely a necessary addition to the field. It is challenging for the authors because I think they are so deep into the details of this protocol, and have put so much time into it, that it is hard to explain to someone who is reading it for the first time. The BMJ Open is a large, general audience, and I wonder if there is a way for the authors to refer to the protocol when there are details, but then speak more generally about it in the paper? Overall it is well written and deserving of publication for sure. Some thoughts -I am interested in the abbreviation PenA. This is not a typical abbreviation I am used to in the US. I think of PennVK as being a type of PCN. If this is typically used in in the UK as an abbreviation, I think it is fine. But otherwise wonder if writing out PCN allergy makes more sense/is easier to read? -Why put antibacterial in parethesis after antibiotic? -I usually thing of it being methicillin-resistant (With a dash) -I know that this is not a typical research paper, but still, I find the pargraph structure of the intro a little challenging to follow and choppy. I think there could be slight modifications in the first 4 paragraphs to bring them into 2 or 3 paragraphs. - recommend separating paragraph 5 into 2 paragraphs at line 19 (We have developed.) -What is the difference between the "pathway" you developed and the work done/reviewed in the systematic review of 69 papers? I think what you are saying is that several people were doing this in a research evaluation, but you wanted to protocolize it in oder to study it from an implementation science point of view?

	-I was really looking for clear statements like "What is know is X, Y, Z" The gap is X, Y, Z. We plan to fill the gap without study, ALABAMA. This could be done in the last 2 paragraphs. I really want you to encourage people who may not understand implementations science to realize why your work is necessary. I see it but other people may not. Methods -Is the nested pilot separate from this study protocol? I am having a hard time figuring out the tense. What has happened, what will happen. I am guessing the nested protocol results have not been published, but that the reference is for the protocol paper? I just found this part confusing. It looks like there is overlap between the nested study and this study. Can you give me more info: "Patients interested in taking part will return an expression of interest form to the trial team." Email, mail, flyer, etc. On Page 10... the word "bespoke" is used a lot. This could be my lack of understanding of the word, but it seems like an odd word to be used there. It sounds like you created a new group of people to help provide patient feedback? What is N.B.1 in the Table 1? You did not yet discuss allergy vs. sensitivity, but point it out as 2 different things in Table 1. I think it makes sense to introduce the idea of sensitivity earlier. I would not consider a "sensitivity" as reason to do allergy testing, I would think this could be a point of counseling. Is this done because people may be unwilling to move forward with PCN without testing? I recommend avoid using the term "chaotic lifestyle" as an exclusion factor. I think you mean they use drugs or they don't show up or maybe they are homeless? Why not just spell that out? What is a chaotic lifestyle? You are at risk for potentially biasing the intervention to get to a subset of the population who would be less likely to experience bad outcomes because of increased wealth, education, etc. In the discussion of "SystemOne": Is this technology that creates a parallel medical record for the research staff? I found this hard to follow. Trial Outcomes -I am surprised that the authors are not using an implementation science framework like RE-AIM. There is no mention of Enola Proctor or other implementation science protocols. They are clearly incorporating effectiveness and implemenetation outcomes. -Are all of the GPs researchers as well? How do the GPs consent the patients for participation if they are not part of the research team? -I would think that the education materials are part of PAAP. I am confused about what PAAP really is at this point in the methods and outcomes. I thought PAAP was the process guiding people through Step 1, 2, 3.

	-The outcome of effectiveness, as I understand, is because most people referred to PAAP will be effectively delabelled and able to get PCN, and the thought is that receiving PCN will help them recover quicker? Is that what the sample size is modeled off of? I am confused because the sample size looks to incorporate "re treatment" rate. I think my confusion is answered when I see the ITT analysis. So the outcome of interest is treatment failure, which the research team feels will occur more often in the people that are not referred to PAAP? -Is the penicillin allergy belief questionaire publically available? -Notably, there is no mention of equity. How do the authors plan to implement with an eye to equity? This could also be addressed with frameworks.

REVIEWER	Solensky, Roland The Corvallis Clinic
REVIEW RETURNED	11-May-2023

GENERAL COMMENTS	1) The major omission in the protocol, which is otherwise very thorough and complete, is a detailed description of how penicillin skin testing will be performed. This should include skin test reagents used (with concentrations), volume of reagents injected intradermally (if prick testing is negative), and criteria used for positive tests. Additionally, I would recommend the testing be performed in duplicate for a trial of this magnitude. 2) Page 7, line 27: "penicillin" should be "penicillins" 3) Page 8, line 7: Reference #15 is the 2010 drug allergy practice parameter, but this is out of date. An updated version of this parameter was published last year, so that should be referenced instead. Additionally, the sentence preceding ref #15 discusses UK and European guidelines, but ref #15 is the US guideline. Also, this updated document recommends direct oral challenge in "low risk" historical penicillin allergy patients, without preceding skin testing. The preceding sentence suggests that guidelines always recommend skin testing before challenge, but that is not true. Therefore, the text should be modified to reflect these new guidelines. 4) Page 11, line 45: Systemic corticosteroids do not inhibit immediate skin testing (unlike patch testing), so there is no reason to disallow them. 5) Is the oral challenge single dose or a graded challenge?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comment	Response
Reviewer #1: Thank you for letting me review this protocol paper. It is very interesting idea and definitely a necessary addition to the field. It is challenging for the authors because I think they are so deep into the details of this protocol, and have put so much time into it, that it is hard to explain to someone who is reading it for the first time. The BMJ Open is a large, general audience, and I wonder if there is a way for the authors to refer to the protocol when there are details, but then speak more generally about it in the paper? Overall it is well written and deserving of publication for sure.	We thank the reviewer for this comment and we have tried to define that the ALABAMA trial is evaluating a complex intervention and what the steps of the penicillin allergy assessment pathway comprises. We have tried to summarise this to better explain that the penicillin allergy assessment pathway (PAAP) not only deals with allergy testing but also provides clinicians with the guidance to de-label participants electronic health records alongside information for participants to understand the importance of penicillin allergy testing and what side effects they may experience. We have added further information to page 6.
I am interested in the abbreviation PenA. This is not a typical abbreviation I am used to in the US. I think of PennVK as being a type of PCN. If this is typically used in in the UK as an abbreviation, I think it is fine. But otherwise wonder if writing out PCN allergy makes more sense/is easier to read?	We're happy to amend to PEN allergy, we'd rather not use PennVK or PCN which is not typically adopted in UK but there is precedent of papers using PenA in the UK: https://pubmed.ncbi.nlm.nih.gov/31225607/ https://bpspubs.onlinelibrary.wiley.com/doi/pdf/10.1111/bcp.14190#:~:text=1%2C2%20Six%20to%2010,incorrect%20following%20comprehensive%20allergy%20testing, Perhaps the BMJ editorial team please advise what their preference is.
Why put antibacterial in parethesis after antibiotic?	Removed as requested.

I usually thing of it being methicillin-resistant (With a dash)	Added dash as requested
I know that this is not a typical research paper, but still, I find the pargraph structure of the intro a little challenging to follow and choppy. I think there could be slight modifications in the first 4 paragraphs to bring them into 2 or 3 paragraphs.	We thank the reviewer for pointing this out. The Introduction has now been amended to improve the flow of information.
Recommend separating paragraph 5 into 2 paragraphs at line 19 (We have developed.)	We have amended this by further explain the development of the PAAP intervention of this trial. Thank you for your insight.
What is the difference between the "pathway" you developed and the work done/reviewed in the systematic review of 69 papers? I think what you are saying is that several people were doing this in a research evaluation, but you wanted to protocolize it in oder to study it from an implementation science point of view?	Thank you for the useful suggestions, these have been incorporated into the revised draft in the introduction.
I was really looking for clear statements like "What is know is X, Y, Z" The gap is X, Y, Z. We plan to fill the gap without study, ALABAMA. This could be done in the last 2 paragraphs. I really want you to encourage people who may not understand implementations science to realize why your work is necessary. I see it but other people may not.	Thank you for the feedback. The introduction has now been amended to highlight what is known and how ALABAMA differs from standard penicillin allergy testing and what we aim to achieve from the ALABAMA study.
Methods	

Is the nested pilot separate from this study protocol? I am having a hard time figuring out the tense. What has happened, what will happen. I am guessing the nested protocol results have not been published, but that the reference is for the protocol paper? I just found this part confusing. It looks like there is overlap between the nested study and this study.	We thank the reviewer for their observation and we have tidied up the tense used. For clarity, the nested pilot seamlessly progressed into the main trial once the stop/go criteria was achieved.
Can you give me more info: "Patients interested in taking part will return an expression of interest form to the trial team." Email, mail, flyer, etc.	Thank you. Further information added on the process of patients returning an expression of interest.
On Page 10... the word "bespoke" is used a lot. This could be my lack of understanding of the word, but it seems like an odd word to be used there. It sounds like you created a new group of people to help provide patient feedback?	Thank you for the feedback. Terminology amended to 'specific'.
What is N.B.1 in the Table 1?	Thank you. N.B amended to 'Please Note'.
You did not yet discuss allergy vs. sensitivity, but point it out as 2 different things in Table 1. I think it makes sense to introduce the idea of sensitivity earlier. I would not consider a "sensitivity" as reason to do allergy testing, I would think this could be a point of counselling. Is this done because people may be	Thank you for the feedback. Due to coding restrictions in the electronic record system (SystmOne), sensitivities are often recorded as allergies. These 'sensitives' often deter GPs from prescribing PCN prior to undergoing PCN testing and de-labelling, thus these patients would be eligible to take part in ALABAMA.

unwilling to move forward with PCN without testing?	
I recommend avoid using the term "chaotic lifestyle" as an exclusion factor. I think you mean they use drugs or they don't show up or maybe they are homeless? Why not just spell that out? What is a chaotic lifestyle? You are at risk for potentially biasing the intervention to get to a subset of the population who would be less likely to experience bad outcomes because of increased wealth, education, etc.	Chaotic lifestyle is used in the UK fairly commonly as part of exclusion criteria. Amending the exclusion and inclusion criteria at this stage imposes great complexity as it is has already by improved by the National REC which would require a substantial amendment and re-consenting all participant remaining in trial.
In the discussion of "SystemOne": Is this technology that creates a parallel medical record for the research staff? I found this hard to follow.	Thank you for the feedback. SystmOne is an electronic record system used in the UK, this section has now been updated to ensure it is clear what SystmOne is used for and how it is used in relation to this trial.
Trial Outcomes	
I am surprised that the authors are not using an implementation science framework like RE-AIM. There is no mention of Enola Proctor or other implementation science protocols. They are clearly incorporating effectiveness and implemenetation outcomes.	The process evaluation as recommended by the MRC development and evaluation guideline facilitates implementation. The focus of ALABAMA is not solely on implementation, the focus is efficacy and cost-effectiveness but is pragmatic to include process evaluation to guide future clinical service implementation. We recognise the scientific framework for implementation science is complex and whilst the suggested RE-AIM framework is excellent, it is not possible within the funding constraints set out by the NIHR, however we hope such work will follow a successful trial outcome.
Are all of the GPs researchers as well? How do the GPs consent the patients for participation if they are not part of the research team?	This has now been amended to clarify the role of the GP.
I would think that the education materials are part of PAAP. I am	This has now been added to the study design section to clarify the Penicillin Allergy Assessment Pathway (PAAP) process.

confused about what PAAP really is at this point in the methods and outcomes. I thought PAAP was the process guiding people through Step 1, 2, 3.	
The outcome of effectiveness, as I understand, is because most people referred to PAAP will be effectively delabelled and able to get PCN, and the thought is that receiving PCN will help them recover quicker? Is that what the sample size is modeled off of? I am confused because the sample size looks to incorporate "re treatment" rate. I think my confusion is answered when I see the ITT analysis. So the outcome of interest is treatment failure, which the research team feels will occur more often in the people that are not referred to PAAP?	Yes, patient health outcomes will be measured by treatment response failure defined by re-presentation with worsening or non-resolving or new symptoms following treatment with an antibiotic up to 28 days after initial antibiotic prescription (including re-prescription of antibiotic within 28 days of an index prescription) for predefined infections over at least one year subsequent to randomisation
Is the penicillin allergy belief questionaire publically available?	No, the questionnaire was created for the purpose of the study and is not yet made publically available.
Notably, there is no mention of equity. How do the authors plan to implement with an eye to equity? This could also be addressed with frameworks.	The way we have identified participants is completely inclusive, as report in generated in SystmOne and everyone with a penicillin allergy and prescription in the last 2 years is invited to take part. We appreciate more proactive follow up of certain groups of participants could be helpful, but resources did not permit this. We have approached the funder for further resources to translate trial material into common languages spoken in our localities and videos to be made that are not literate in their own language. We have not included this as funding has not been approved yet.
Reviewer 2 Comment	**Response**
The major omission in the protocol, which is otherwise very thorough and	Thank you for the feedback. The SOP for skin prick and intradermal allergy test as well as the SOP for oral challenge test has been added as appendices. (Appendix 3 & 4)

complete, is a detailed description of how penicillin skin testing will be performed. This should include skin test reagents used (with concentrations), volume of reagents injected intradermally (if prick testing is negative), and criteria used for positive tests. Additionally, I would recommend the testing be performed in duplicate for a trial of this magnitude.	
Page 7, line 27: "penicillin" should be "penicillins"	Thank you for spotting this, it has been updated.
Page 8, line 7: Reference #15 is the 2010 drug allergy practice parameter, but this is out of date. An updated version of this parameter was published last year, so that should be referenced instead. Additionally, the sentence preceding ref #15 discusses UK and European guidelines, but ref #15 is the US guideline. Also, this updated document recommends direct oral challenge in "low risk" historical penicillin allergy patients, without preceding skin testing. The preceding sentence suggests that guidelines always recommend skin testing before challenge, but that is not true. Therefore, the text should be modified to reflect these new guidelines.	Thank you for bringing this to our attention. I have updated the manuscript with a reference to the updated version of the drug allergy practice parameter. The sentence preceding reference #15 has been updated to make it clear that reference 14 and 15 relate to UK and US guidelines only.

Page 11, line 45: Systemic corticosteroids do not inhibit immediate skin testing (unlike patch testing), so there is no reason to disallow them.	We can't change the exclusion criteria at this stage. Systemic corticosteroids interfere with the OCT and that is why it forms part of the exclusion criteria.
Is the oral challenge single dose or a graded challenge?	A risk stratification will be completed, and if the patient requires a skin prick test before proceeding to oral challenge testing, then a graded challenge will be performed. If the patient can proceed directly to the oral challenge test, then a single dose will be administered.

VERSION 2 – REVIEW

REVIEWER	Wurcel, Alysse G Tufts University School of Medicine
REVIEW RETURNED	26-Jun-2023

GENERAL COMMENTS	Well done. Great addiction to the field!

REVIEWER	Solensky, Roland The Corvallis Clinic
REVIEW RETURNED	07-Jul-2023

GENERAL COMMENTS	The authors modified the manuscript according to my recommendations.