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Supplementary appendix

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Supplementary Appendix Content

ALABAMA Trial Research Group

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Trial Title: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance.

Internal Reference Number / Short title: ALABAMA: **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resist**A**nce

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Trial Title	Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance. Trial Protocol.	
Internal ref. no. / short title	ALABAMA: **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resist**A**nce	
Trial Design	Multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested-pilot trial	
Trial Participants	Adults (≥18 years of age) with a penicillin allergy record	
Planned Sample Size	Sample size of the trial is between 656 and 848 (including the 96 from the nested pilot)	
Planned Trial Period	5 years	
	Objectives	**Outcome Measures**
Primary Outcome	Effects of PAAP on penicillin prescribing	The proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (APPENDIX G) up to 12 months post randomisation (SystmOne report/primary care notes review/secondary care notes review/report, patient follow-up calls)
Secondary Outcomes	1. To determine whether the PAAP intervention is clinically effective in improving patient health outcomes.	1. Treatment "response failure" defined as: 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 (SystmOne report, diary), up to 12 months post randomisation.
	2. Effects of PAAP on symptom duration.	2. Duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment (diary/research nurse phone calls)
	3. Effects of PAAP on total antibiotic prescribing	3. Total antibiotic use (measured by number of days treatment, number of prescriptions and Defined Daily Dose (DDD).), and analysed by penicillin/non-penicillin and antibiotic class (SystmOne report/primary care notes review/secondary care notes review).

	4. Effects of PAAP on hospital admissions and length of hospital stays	4. Number of hospital admissions and length of hospital stays (Hospital Episode Statistic (HES)/secondary care notes review)
	5. Effects of PAAP on mortality rates	5. Mortality rates between intervention arms (primary care notes review/secondary care notes HES-ONS/SystmOne Report)
	6. Effects of PAAP on Meticillin-resistant *Staphylococcus aureus* (MRSA) infection/ colonisation	6. Number of patients with MRSA infection/new colonisation (primary care notes review/secondary care notes review/SystmOne report)
	7. Effects of PAAP on *Clostridioides difficile* infection	7. Number of patients with *Clostridioides difficile* infection (SystmOne report/primary care notes review/secondary care notes review)
	8. To explore patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use.	8. Healthcare professional and patient interviews
	9. (Process evaluation) To explore patient and clinician experiences of trial procedures.	9. Healthcare professional and patient interviews
	10. To measure the influences on patient behaviour change regarding consuming penicillin following a negative test result.	10. Change in self-reported behaviour and influences on behaviour by patients.
	11. Cost effectiveness for the PAAP intervention compared to usual care	11. Self-reported health/QoL outcome: EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 1 year. For those that receive antibiotics for pre-defined infections, EQ5D-5L will be collected on day 2-4 and day 28-30 after antibiotic treatment. NHS health resource use will be measured through primary and secondary care notes review, and through linked HES data.

	12. a) Effects of PAAP on de-labelling at 3 months post randomisation	12. a) The proportion of ALABAMA participants whose labels are removed from the primary care medical eHR record allergy section at 3 months post randomisation.
	12. b) Effects of PAAP on de-labelling up to 12 months post randomisation	12. b) The proportion of ALABAMA participants whose labels were removed at 3 months and remain removed from the primary care medical eHR record allergy section up to 12 months post-randomisation.
Exploratory outcomes	13. Safety outcomes	13. A descriptive analysis will be performed looking at the safety of de-labelling in the intervention group
	14. Effects of PAAP on all outcomes for follow up past 12 months	14. Descriptive analysis using data captured in the notes review CRF

2. ABBREVIATIONS

DDD	Defined Daily Dose
AMR	Antimicrobial resistance
AE	Adverse Event
CI	Chief Investigator
CDI	*Clostridioides difficile* infection
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
DCF	Data Clarification Form
DMP	Data Management Plan
eHR	electronic Health Records
GCP	Good Clinical Practice
GP	General Practitioner
HCAI	Healthcare associated infection
HES	Hospital Episode Statistics
HRA	Health Research Authority
ICF	Informed Consent Form

MRSA	Meticillin-resistant *Staphylococcus aureus*
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
OCT	Oral Challenge Test
ONS	Office for National Statistics
PAAP	Penicillin allergy assessment pathway (the entire process from patient selection to updating of electronic health records (de-labelling) and behaviour change materials to aid GP prescribing of penicillins in patients who have been de-labelled.)
PAT	Penicillin Allergy Testing (the process of history taking, test selection and undertaking skin testing and/or oral challenge testing)
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
ST	Skin testing
SystmOne	Electronic health record system developed by TPP
SWAT	Study within a Trial
TPP	The Phoenix Partnership (company that developed and operates SystmOne)
ALABAMA Unit	ALABAMA-specific organisation within SystmOne to facilitate trial processes such as electronic referrals.

3. BACKGROUND AND RATIONALE

The importance of antibiotic resistance (AMR) and the need to reduce its impact is well recognised.[1] Penicillins are the most commonly prescribed antibiotics[2] and remain first-line therapy for many common infections. A record of penicillin allergy has a marked effect on antibiotic prescribing.[3-5] Penicillin allergy records are common because side effects and symptoms related to the infection requiring antibiotic treatment are often mislabelled as allergies. About 6-10% of the UK population self-report a penicillin allergy but, importantly, fewer than 10% of these patients are truly allergic[6-8]. Consequently, a significant proportion (~9%) of the population are potentially restricted access to highly effective penicillins. Penicillin allergy records are associated with AMR; evidence from the UK and USA suggests that patients with a penicillin allergy record are more likely to acquire multi-drug resistant bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA).[9-11] Preliminary investigations of 2 million adult primary care patients found that a lack of response to treatment and MRSA were significantly more common in patients with a penicillin allergy record.[12]

The focus of ALABAMA is 'false positive' records of penicillin allergy, how these affect prescribing and whether a complex intervention aimed at verifying these records is clinically/cost effective. Patients with

a penicillin allergy are usually not prescribed penicillins but instead receive alternative, broad-spectrum antibiotics, which may lead to suboptimal therapy, be associated with poorer longer-term outcomes, and contribute to AMR.[8 11 13] Our preliminary research found macrolide, tetracycline, cephalosporin, quinolone and clindamycin prescribing were all more common in patients with a record of penicillin allergy compared to those without, and that antibiotic prescriptions were almost twice as frequent in patients with a penicillin-allergy record.[12] These differences were not explained by age, sex, or comorbidity. Limited evidence from USA suggests that antibiotic-allergies affect health outcomes; increasing mortality, length of stay and costs.[8] The large discrepancy between reported and true allergy rates suggests that introducing a *'pre-emptive'* penicillin allergy assessment pathway (PAAP) for patients who are more likely to receive antibiotics, could impact upon antibiotic prescribing, yield patient benefits, limit AMR/Healthcare associated infection (HCAI) and deliver NHS cost savings.

Assessment of patients with penicillin allergy in specialist clinics is already provided within the NHS, but most who are eligible are not offered the service because of a lack of capacity.[14] Current penicillin allergy testing in many immunology/allergy clinics is performed over at least two clinic visits; the first, to undertake history and performing the ST; the second to assess reactions and undertake oral challenge testing (OCT) followed by communication of results. The allergy history is important to determine if the allergy history is spurious, of uncertain risk, low risk or high risk of true penicillin allergy.[14] Skin testing and OCT may follow.

The ALABAMA trial approach will be different from standard NHS practice in two ways:

1) Streamlining the process by undertaking initial elements (history) in the community/via telephone, and developing a "one stop shop" single hospital clinic visit for specialist immunology assessment (skin testing and/or OCT).
2) Pre-emptive testing will be undertaken in patients with a higher risk of being prescribed antibiotics in primary care, rather than in the context of an acute allergic reaction or soon after a reaction.

If the evaluation finds that this more 'patient-friendly' approach to allergy testing is more efficient, this would enable more patients to be tested within current resources. The proposed trial testing will take place in secondary care, in an immunology clinic, or a clinic set up specifically for penicillin allergy testing. It is important to note that pre-emptive allergy testing as outlined in the ALABAMA PAAP is different from testing a patient who has an absolute need for a penicillin to treat a life-threatening infection. The risk-benefit analysis is different in these two situations and a more cautious approach has been taken in the ALABAMA PAAP.

PAAP has deliberately been designed as an efficient one-stop procedure that will involve [1] medical history in primary care to either [i] exclude those at risk of anaphylaxis or other severe adverse reactions, or [ii] indicate a referral to secondary care and [2] half a day in clinic and potentially a three-day post clinic course of oral antibiotics. The PAAP differs from current standard UK and European guidelines in that it offers patients assessed as 'low risk' of true allergy an abbreviated test consisting of direct oral challenge, with no preceding skin tests. Whilst the gold standard test with which to establish tolerance to penicillin is an oral challenge, current UK and European guidelines advise that patients should first be skin tested, using prick or intradermal tests, or both. This identifies patients who are IgE-sensitised, and provides risk stratification for progression to a challenge test. Skin tests have a negative predictive value (NPV) approaching 100%, and patients who do not react to prick or intradermal tests are therefore unlikely to

have a severe reaction on challenge. However, the interpretation of positive skin tests is less clear; these patients are generally not offered a challenge test and so the positive predictive value (PPV) is hard to determine. The PPV is generally accepted to be less than 50% based on a limited numbers of prospective studies, and on outcomes from accidental re-exposure. Increasingly, the evidence demonstrates that patients can be risk stratified for a challenge test on the basis of history alone. Where symptoms are not severe, not suggestive of an IgE-mediated reaction, are vague, or historic, the utility of skin testing is low and a direct oral challenge may be safe and appropriate. This approach is already used routinely for children in the UK and several studies have demonstrated safety and efficacy in adults. Patients whose histories are not clearly low risk will still undergo skin testing, and only proceed to oral challenge if this is negative.

The PAAP will be divided into three stages which can initially be undertaken in a primary care setting but move to a hospital clinic for penicillin allergy testing. Each stage has been risk assessed based on published data and expert opinion to minimise risk of harm and keep the costs of the pathway down. The nested-pilot data may allow a subset of patients to just be tested by oral challenge.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective Effects of PAAP on penicillin prescribing	**Primary Outcome Measures** The proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (APPENDIX G) up to 12 months post randomisation (SystmOne report/primary care notes review/secondary care notes review/report, patient follow-up calls)	Up to 12 month post-randomisation Primary Endpoint: Up to 12 months post randomisation
Secondary Objectives 1. To determine whether the PAAP intervention is clinically effective in improving patient health outcomes.	**Secondary Outcome Measures** 1. Treatment "response failure" defined as: Re-presentation with worsening or non-resolving or new symptoms following treatment with an antibiotic up to 28 days	1. Timepoint: Each antibiotic prescription for predefined conditions prompts diary and patient reported outcomes collected for up to 28 days (or until symptoms resolve). Day 28

	after initial antibiotic prescription (including re-prescription of antibiotic within 28 days of an index prescription) for predefined infections (SystmOne report), up to 12 months post randomisation (primary and secondary notes review)	– 30 telephone call, will capture the primary outcome data as well. Primary Endpoint: Up to 12 months post randomisation
2. Effects of PAAP on symptom duration.	2. Duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment (diary/research nurse telephone calls)	2. Day 1 – 28 symptom diary after the first antibiotic prescription identified as a primary event. This will also be collected at day 28-30 by phone call for every antibiotic prescription identified as a primary event
3. Effects of PAAP on total antibiotic prescribing	3. Total antibiotic use (measured by number of days treatment, number of prescriptions and Defined Daily Dose (DDD)) and analysed by penicillin/non-penicillin and antibiotic class (SystmOne report/primary care notes review/secondary care notes review).	3. Up to 12 month post-randomisation
4. Effects of PAAP on hospital admissions and length of hospital stays	4. Number of hospital admissions and length of hospital stays (Hospital Episode Statistic (primary care notes review/secondary care notes HES-ONS/SystmOne Report)	4. Up to 12 month post-randomisation (continues annually until end of trial).
5. Effects of PAAP on mortality rates	5. Mortality rates between intervention arms (HES/ONS/SystmOne report, primary and secondary care notes review)	5. Up to 12 months post-randomisation

6. Effects of PAAP on Meticillin-resistant *Staphylococcus aureus* (MRSA) infection/ colonisation	6. Number of patients with MRSA infection/colonisation (primary and secondary care notes review/SystmOne report)	6. Up to 12 month post-randomisation
7. Effects of PAAP on *Clostridioides difficile* infection	7. Number of patients with *Clostridioides difficile* infection (primary & secondary care notes review, SystmOne report)	7. Up to 12 month post-randomisation
8. To explore patient and clinician views and experiences of penicillin allergy testing, test results and future antibiotic use.	8. Healthcare professional and patient interviews	8. Qualitative interviews for healthcare professionals once their practice has recruited a proportion of patients, or once they have finished recruiting to the trial, and interviews with healthcare professionals responsible for PAT once all testing is completed. Qualitative interviews for participants once they have received their PAAP result
9. (Process evaluation) To explore patient and clinician experiences of trial procedures.	9. Healthcare professional and patient interviews	9. Qualitative interviews for healthcare professionals once their practice has recruited a proportion of patients to the trial, or once they have finished recruiting to the trial, and interviews with healthcare professionals responsible for PAT once all testing is completed. Qualitative interviews for participants once they have received their PAAP result
10. To measure the influences on patient behaviour change regarding consuming penicillin following a negative test result.	10. Change in self-reported behaviour and influences on behaviour by patients.	10. Participant allergy belief questionnaire (Baseline, D28 – 30 post-PAAP, D2 -4 post-antibiotic episode)

11. Cost effectiveness for the PAAP intervention compared to usual care	11. Self-reported health/QoL outcome: EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 1 year. For those that receive antibiotics, EQ5D-5L will be collected on day 2-4 and day 28-30 after antibiotic treatment. NHS health resource use will be measured through primary and secondary care notes review and linked HES data.	11. EQ-5D-5L™ will be used as a standardised instrument for measuring health outcome at baseline and 12 months post randomisation and on day 2 – 4 and day 28-30 post antibiotic episode (end point is 12 months post randomisation). Costs will be measured at 12 months and, through model-based extrapolation, up to 5 years after randomisation.
12. a) Effect of PAAP on de-labelling at 3 months post randomisation	12. a) The proportion of ALABAMA participants whose labels are removed from the medical eHR record allergy section. (primary care notes review)	12. a) At 3 months post randomisation
12. b) Effect of PAAP on de-labelling up to 12 months post randomisation	12. b) The proportion of ALABAMA participants whose labels were removed and remain removed from the medical eHR record allergy section up to 12 months post-randomisation. (primary care notes review)	12. b) up to 12 months post randomisation (S
13.Safetyoutcomes (Exploratory Outcome)	13. A descriptive analysis will be performed looking at the safety of de-labelling in the intervention group	13. Up to 12 months post randomisation
14. Effects of PAAP on all outcomes for follow up past 12 month	14. Descriptive analysis using data captured in primary and secondary care notes review CRF/SystmOne report	14. Until the end of the study

4.1. Feasibility Outcomes of Nested Pilot Trial

In addition to the outcomes of the trial, the nested pilot trial will also collect the following outcomes to address the safety, acceptability and practicality of delivering PAAP:

1. To assess the feasibility of recruitment by reviewing the number of patients per practice per month enrolled into trial (trial log, trial manager) such that at least 8 GP practices are recruited, and 96 patients identified and recruited during Stage 1 recruitment period.

2. Details of suitable patients with a penicillin allergy record for ALABAMA (feedback from practice that suitable lists generated with ease) to evaluate the performance of electronic identification search to identify suitable patients from eHR.

3. Number of exclusions by reviewing GP screening logs to assess willingness of GPs to refer to PAAP.

4. Number of patients attending PAAP clinic/Number patients randomised to PAAP (trial logs/SystmOne report) to assess willingness of patients to undergo testing;

5. Number of patients undergoing PAAP who have their electronic health records updated with the test result (SystmOne report/primary care notes review) to assess willingness of GPs to update eHR records.

6. Number of patients with negative PAAP result prescribed penicillin for condition requiring penicillin as first line therapy (SystmOne report/primary care notes review) to assess willingness to prescribe penicillin to patients with negative test results.

7. Penicillin consumption (diary/research nurse phone calls)/penicillin prescribed/SystmOne report/primary care notes review/secondary care notes review) to assess willingness of patients to receive penicillin after a negative test result.

8. Number of safety events captured through research nurse telephone calls compared to notes review to assess optimal PAAP safety monitoring strategy.

9. Operational assessment of number patients tested/month in PAAP clinic compared to number of patients randomised to PAAP per month, time from randomisation to PAAP appointment (TPP) to assess patient flow from recruitment to PAAP.

10. Details of prescription of penicillins in secondary and tertiary care/ Number events in secondary or tertiary care necessitating prescription of antibiotics where a penicillin would have been the first-line therapy (SystmOne report/primary care notes review/secondary care notes review) to assess communication of changes to penicillin -allergy records across the health sector (e.g. to secondary/tertiary care) and to assess feasibility of prescribing data capture.

11. CRF completion rate for participants with antibiotic prescription to assess data quality of trial CRFs completed by GP, and trial team.

12. Diary return rates, data expected and completeness of diary to assess quality of diary completion.

13. Effectiveness of electronic data capture e.g. antibiotic prescribing information (SystmOne report generated reports) and manual checks of health records (notes review) to assess the feasibility and quality of electronic means of capturing secondary trial outcome data;

14. Number of events resulting in re-prescription of antibiotics within 28 days of index prescription and duration of symptoms rated ‘moderately bad’ or worse (up to 28 days after initial antibiotic prescription) (Diary/SystmOne report/Primary care notes review/Secondary care notes review) to assess

whether diaries are suitable to capture re-prescription rates and duration of symptoms rated 'moderately bad' or worse.

15. Percentage of antibiotic prescriptions for which a clinical infection code is allocated (SystmOne report) to assess availability of clinical indication (type of infection) for each antibiotic prescription from electronic health records.

16. Attrition rate, including loss to follow-up or withdrawal, and reasons to assess factors contributing to this.

17. Antibiotic prescribing frequency/treatment response failures to assess the estimated base rate used for sample size calculation was adequate.

5. TRIAL DESIGN

This is a multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested pilot trial.

Potentially eligible patients will be identified during a search of their electronic health records at their general practice. The electronic search criteria will be developed centrally by the research team in partnership with TPP and made available for running locally on SystmOne e.g. by practice managers, LCRN Research Nurse Team or Leeds CCG Pharmacy Technician team. Potential participants will be sent an invitation pack and those interested in taking part will return an expression of interest form to the trial team. They will be telephoned and booked into an either face to face or telephone appointment with their GP or the trial team at a time that is convenient to them. During this appointment, their GP, or a delegated member of the staff, will confirm their eligibility to participate and consent them to take part in the trial. The participants will then receive another telephone call from a member of the trial team to complete the baseline case report form (CRF). At this point, the participants will be asked if they have taken any antibiotics in the previous two weeks, if they have the randomisation/baseline call will be postponed until the participant has been free of antibiotic use for two weeks.

Once the baseline CRF is complete the participants will be randomised to usual care or the PAAP intervention arm. Those randomised to the PAAP intervention arm will be booked into an appointment at the local hospital clinic, where they will have penicillin allergy testing.

Participants recruited during the nested pilot phase will be followed up for an initial 4 months for the feasibility outcomes, during which they will be contacted monthly by the trial team. Following a "stop go" assessment, all nested pilot study participants will subsequently be followed up for at least 12 months in the main trial to align their follow-up with participant recruited to the main trial.

Regular reports will be run in the ALABAMA unit to identify participants who have been prescribed an antibiotic, for any cause, in the previous 7 days. A member of the research team will send an alert to the trial research nurses team who will then follow the participant up for the duration of the associated infection. The research team will designate an antibiotic prescription as a 'primary event' if the patient is prescribed an antibiotic for a pre-defined list of infections (refer to appendix G). Participants receiving antibiotics for the first primary event since randomisation, will be asked to complete a symptom diary. At the end of the follow up period their electronic health records will be reviewed to ensure we have captured all antibiotic events. For collection of trial outcome data, all trial participants will have hospital episode

statistics and mortality data collected, primary care health records reviewed, and secondary care health records if required.

Throughout this process general practice staff and participants will receive behaviour change intervention materials as outlined in section 9.

For the process evaluation, an allergy belief questionnaire will be sent to all patient participants. The questionnaire will measure influences on patient antibiotic consumption. Interviews will also be completed with a subset of healthcare professional and patient participants. A subset of patient participants will be invited to take part in an interview once they have completed the PAAP and received their allergy test result. Interviews will sample patients who have both positive and negative allergy tests with a focus on the latter, and patients in the control arm. A subset of healthcare professionals from participating practices or from those participating in the trial in secondary care sites will be invited to take part in an interview once their practice has recruited a proportion of patients to the trial or when they have finished participating in the trial.

See appendix A for trial flowchart.

6. PARTICIPANT IDENTIFICATION

6.1. Trial Participants

Participants who are over 18 with a record of a penicillin allergy.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial
- Male or Female, aged 18 years or above
- Current penicillin allergy (or sensitivity) record of any kind in their electronic health record
- Prescribed systemic antibiotics, either: penicillin, cephalosporin, tetracycline, quinolone, macrolide, glycopeptide, aminoglycoside, oxazolidinone, monobactam or carbapenem class antibiotic or fosfomycin, nitrofurantoin, trimethoprim, clindamycin, rifampicin, colistin, metronidazole in the previous 24 months

N.B.1 Patients who have been formally tested for penicillin allergy in the past and been found not to be penicillin allergic but still have a medical record indicating a penicillin allergy, are eligible for the trial.

6.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Life expectancy estimated <1 year by GP
- Unable to attend hospital clinic where allergy testing takes place
- Unsuitable for entry into testing pathway because:
    - Allergy history consistent with anaphylaxis to penicillin
    - History of toxic epidermal necrolysis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms (DRESS) or any severe rash which blistered or

needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin
- Has been formally tested for penicillin allergy in the past and been found to be penicillin allergic
- History of brittle/severe asthma or has had a course of steroids in the past 3 months for asthma or unstable coronary artery disease, or other severe/poorly controlled skin conditions
- Considered unsuitable for trial participation by the GP e.g. because of chaotic lifestyle

- Pregnant
- Breastfeeding mothers
- Currently taking beta blocker medication, and unable to temporarily withhold these on the day of penicillin allergy testing
- Currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pre-testing
- Currently taking antihistamines and unable to temporarily withhold these for 72 hours pre-testing

GPs may also want to exclude vulnerable patients who are deemed to be unsuitable to participate for other reasons such as, but not limited to, terminal illness, reliability, mental illness, learning difficulties, anxiety, and other family circumstances.

N.B.1 Patients that are currently taking medicines with antihistamine properties that cannot be temporarily withheld, or patients with isolated dermographism, may still be eligible to participate but will need to be discussed with the research team prior to consent.

N.B.2 Pregnancy and breastfeeding exclusion criteria are only applicable at screening (due to potential risks of PAT); these patients would not need to be withdrawn if in follow up.

7. TRIAL PROCEDURES

Please see the schedule in Appendix D.

All trial procedures will be the same for the nested pilot trial and the main trial, unless stated.

7.1. Promotion

ALABAMA will be promoted in the areas where there are general practices that are open to recruitment. Trial promotion will comprise posters in the general practices, primary care centres and other appropriate local sites (e.g. neighbouring pharmacies). ALABAMA will also be promoted by practice assistants during triage on the telephone, and, if thought necessary, through radio and other media advertisements. All promotion materials will inform people that if they have a record of penicillin allergy, they may wish to contact their GP Practice about participation in the ALABAMA trial and to find out information relating to their local recruitment centre.

Potential eligible patients might also be approached to take part in ALABAMA by their GPs during their routine primary care consultations, by pharmacists or by healthcare workers during hospital consultations by handing out information sheet.

7.2. Site Training

General practices will receive training in trial procedures and identifying potential participants. In addition, practice staff will receive an "Information pack" on the PAAP to increase knowledge about allergy testing and motivation to refer patients (see Section 9).

7.3. Screening and Eligibility Assessment

The electronic health records of each participating general practice will be screened for potential participants using a SystmOne report. This list of potentially eligible patients will be sent an invitation letter via post or email by their general practice and asked to return an expression of interest form to the trial team via post or electronically, if they are interested in taking part. A non-responder letter may also be used at least a month after the initial mail out to re-contact any potential participants who do not reply to the initial invitation. Practice staff (or authorised staff delegated this responsibility on behalf of the practice, such as the CCG Medicines Management Team, or CRN Nurses) may also telephone invited patients to discuss their potential participation in the trial. After invitations letters have been sent out, GP practices may be asked to text the potential participants reminding them to consider the trial. Additional eligible patients that attend clinic requiring antibiotics, can be invited by their GP, or delegate, to take part by providing the patient with a copy of the Patient Information Sheet (PIS) and an invitation letter.

Once an expression of interest form has been received, the participant will be booked into a recruitment appointment with the recruiting GP, or a delegated member of staff, at a time that is convenient to them, but as soon as possible to avoid any unnecessary delays. Patients will be offered either a telephone or face-to-face appointment to go through the consent with either their GP, other clinicians, or authorised staff who are delegated this responsibility on behalf of the practice, such as the CRN Nurses. Participants will receive a reminder text message from their GP practice one week and 48 hours before their telephone call or face-to-face appointment. At this appointment their eligibility will be confirmed before continuing on with the informed consent.

7.4. Informed Consent

Informed consent will be taken either during the recruitment visit or via a telephone call with the GP or a member of the research team. Patients will be given the choice between these two options. If the participant chooses the face-to-face consent visit, they must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any trial specific procedures are performed. If the participant chooses verbal consent, the trial team member or GP will complete the ICF on behalf of the participant and send a copy of the ICF to the participant in the post.

Written and verbal versions of the Participant Information Sheet (PIS) and Informed Consent will be presented to the participants as part of the information pack detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the potential risks involved in taking part. It will be clearly stated that the participant is free to withdraw from

the trial at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and will be given the opportunity to question the Investigator, their GP, or other independent parties to help them decide whether they will participate in the trial or not. For participants who choose face-to-face consent, written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. Alternatively, for participants who elect to provide verbal consent, this will be carried out over the phone. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. All staff working on ALABAMA shall be trained to do so in accordance with the conditions and principles of Good Clinical Practice. A copy of the completed Informed Consent Form (ICF) will be given/sent to the participant. The original form will then be retained in the trial site file at the trial site.

For participants who are unable to read and respond to the questions asked by the research team, i.e. when English is not their first language or they have an impairment that makes communication difficult, a participant will be able to identify a Trial Partner, prior to consent, who can help them navigate trial documents and processes. The patient can then contact us, with the help of a trial partner, to let us know that they wish to use a trial partner and to provide the trial partner's name and contact details. The telephone consultation will be completed via Microsoft Teams to ensure that both the patient and trial partner can be identified. This will not be a requirement for trial participation

The trial partner will be able to assist the participant in completing screening, consent, baseline, randomisation, testing (if applicable) and follow up by providing information to them and interpreting their answers. A letter will be issued to Trial Partners, informing them of the trial, notifying them that the participant has nominated them for this role. The trial partner may be a family member, friend, carer, or other suitable person. The name and contact details of the trial partner will be saved on Sentry and will only be accessible by the research team. If a trial partner cannot be identified, every effort will be made to ensure the patient can participate by providing a service to interpret research questions and ensure they can communicate with the research team.

Patients and GPs invited to take part in telephone interviews will be provided with PISs and ICFs specific to the qualitative component of the trial. A written Participant Information Leaflet (version) and Informed Consent Form (ICF, version) will have been sent by post or email to, and read by, the participant, ideally at least 24 hours before the oral consent is sought. The oral consent script and the content of the ICF will be read to the participant, who will respond to each of the points of the IFC, and will be audio recorded. The audio recording of the oral consent obtained will be then transferred from the audio recorder and stored (separately from the interview transcript) in a password-protected file on a university computer. The recording of the oral consent will not be sent to the transcribing company.

The GP practice will confirm, via the SystmOne electronic patient health record, that they have consented a patient. The GP will then refer the patient to the ALABAMA research team via the ALABAMA Unit within SystmOne. This will trigger the research team to be able to call the consented persons to check eligibility, safety, progress to randomisation and, if appropriate, schedule an appointment for a penicillin allergy test.

7.5. Baseline Assessments

This will be completed during the telephone call with the participant. For all participants this will include information on:

- EQ-5D-5L
- Penicillin allergy history (Stage 1 penicillin allergy test)
- Patient questionnaire on allergy beliefs

Medical history will be collected through a notes review/SystmOne report (age, number of antibiotic prescriptions/year, and number of QOF registered diseases). Demographic features including ethnicity will be captured at baseline.

Text message reminders may be sent to the patient to contact the study team if we are unable to reach them to complete baseline assessments.

7.6. Randomisation

During their call with the research team, participants will be asked if they have taken any antibiotics in the previous two weeks; if they have, the randomisation/baseline call will be postponed until the participant has been free of antibiotic use for two weeks. The research team will arrange another call to take place when the participant has been free of antibiotic use for two weeks. During the call, the participants will be asked to complete the baseline assessment and the member of the research team will perform randomisation. Randomisation will be performed using Sortition (PC-CTU's in-house online randomisation system) according to the current version of the SOP PC-CTU_SOP_IT104. Allocation will be minimised by general practice, age, number of antibiotic prescriptions up to 24 months prior to randomisation, and number of QOF registered diseases, to ensure balance of allocation of these baseline covariates. Patients will be randomised to either usual care (with subsequent monitoring for antibiotic prescriptions and follow-up for trial outcomes as determined by the clinical indication for antibiotics) or the PAAP intervention arm using an allocation ratio of 1:1. Both the participants and the recruiter will know which arm they have been randomised to. The trial statistician will remain blinded to treatment allocation when performing the final analysis. Unblinding of the allocation will take place in accordance of the SOP PC-CTU_SOP_ST105.

Patients randomised to the PAAP trial arm will be posted and/or emailed the "Pre-test Intervention Booklet" with their hospital appointment letter (see section 9).
Text message reminders may be sent to the patient to contact the study team if we are unable to reach them for randomisation.

N.B. Patients randomised to the PAAP trial arm, who do not attend an appointment for PAT, will continue to be followed up unless consent is withdrawn.

7.7. Penicillin allergy test Appointment

Please see schedule in Appendix B.

Those in the PAAP intervention arm will be invited to attend an appointment at the local hospital clinic. Participants will receive a text message one week and 48 hours before their appointment to remind them to attend the clinic. At this appointment they will complete stage 2 and 3 of the penicillin allergy test:

- Stage-2 assessed for skin testing (ST) and ST done or straight to stage 3
- Stage-3 oral challenge test (OCT)

Text message reminders may be sent to the patient regarding contacting the study team if we are unable to reach them to arrange a penicillin allergy test appointment.

All patients completing penicillin allergy testing will receive a letter from the local hospital clinic giving the results of the penicillin allergy test after their appointment. In addition to the letter, patients who have tested negative for penicillin allergy will receive the "Post-test Intervention Booklet" and "Patient Intervention Card" (see section 9). Materials will be sent by post and/or email.

Additionally, all participants in the PAAP arm will be called by the trial team at days 4-6 and 28-30 post testing to collect safety data. During the call at days 28-30 patients will again complete the patient questionnaire on allergy beliefs.

Practices will be informed of the test result and instructed to update the participant's electronic health records accordingly.

The table in Appendix C provides more information on the penicillin allergy test.

7.8. Subsequent Participant Contact

Feasibility outcomes only:

Patients enrolled in the nested pilot phase will be contacted monthly for four months to review safety and confirm whether or not they have received an antibiotic.

Main trial outcomes:

When any patient attends a future consultation, prescribers will be made aware of their penicillin allergy status and (potentially) revised or confirmed allergy status via their electronic health record. The health record of each patient will contain a link to the "Information pack" for prescribers as a reminder (see Section 9).

If and when they attend their general practice and receive an antibiotic, the trial team will be alerted via regular SystmOne reports run by the research team.

Participants in the main trial will be asked to complete a symptom diary when they receive an antibiotic for a pre-defined list of infections (refer to Appendix G) for the first time after randomisation.

They will be asked to complete a daily diary (paper or electronic, whichever they prefer) detailing their:

- One or two predominant presenting symptoms
- Symptom severity. The predominant symptoms will be scored daily on a scale from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be) the scale is taken from a validated measure[15]

- Antibiotic consumption and any side effects

The diary will be completed for 28 days or until the patient's symptoms are a 'slight problem' or less (scoring 2 and below) and they have stopped their course of antibiotics.

Two to four days after the GP appointment, a member of the trial team will call the participant to remind/assist them to complete the diary (if first primary event since randomisation) and will complete the patient questionnaire on allergy beliefs and safety review.

Participants will receive a text message on day 7, 14 and 21 to remind them to complete their diary.

If participants decide to complete their diary online, they will also receive daily email reminders to complete their diaries. The reminders will stop and diaries will be deactivated if their symptoms are mild, they complete the course of their antibiotics or if they reach day 29.

28 – 30 days after this appointment a member of the trial team will call the participant to capture the primary outcome data, safety review, and complete EQ-5D-5L questionnaire.

Twelve months after randomisation a member of the trial team will call the participant to complete their EQ-5D-5L questionnaire.

7.9. Notes Review

Participants recruited during the nested pilot phase will have their electronic health record interrogated at the 4-month time point from randomisation, to collect data on all antibiotic prescriptions given during the follow-up period with the read codes for the indication for the prescription or clinical indication (if no read code is entered). We will also capture information on any participants that are admitted to hospital (HES data) and capture details of antibiotic prescriptions during their admission (notes review).

Following completion of the follow up period from randomisation , all participants will have their electronic health record interrogated (Primary and Secondary care notes review/SystmOne report) for data on all antibiotic prescriptions given during the follow-up period with the read codes for the indication for the prescription or clinical indication (if no read code is entered). We will also capture information on any participants that are admitted to hospital (HES data), capture details of antibiotic prescriptions during their admission (secondary care notes review) and mortality data (HES/ONS/Primary and Secondary care notes review).

The SystmOne ALABAMA unit will remain in existence for 10 years after the close of the trial, subject to further funding and subsequent ethics approval, to carry out a trial of long-term outcomes. These outcomes would be based on the same routinely collected outcome data as in the ALABAMA trial. No further patient contact of any kind would be required and this long-term outcome data would be entirely based on an extract of routinely collected clinical data. Patients will be consented for this as part of the current ALABAMA trial consent process.

7.10. Interviews

A subset of participants and healthcare professionals taking part in the nested pilot trial and then also the main trial will be invited to take part in interviews to understand their experiences of taking part in the

trial and of referring to/attending for penicillin allergy testing and subsequent antibiotic prescribing/consumption.

Only participants who have indicated that they are happy to be contacted for an interview on the trial consent form will be invited. We will seek to interview approximately 10-15 patients who underwent penicillin allergy assessment as part of the nested pilot study and 2-5 patients who were randomised to the control arm. We may interview patients randomised to PAAP but who did not attend for penicillin allergy testing if necessary. For the main trial, we will undertake a process evaluation and will interview approximately 20-30 patients who are invited to attend for penicillin allergy assessment (a purposeful sampling framework based on age, gender, years since allergy diagnosis and penicillin allergy test result). Participants will be contacted by telephone by a member of the research team to ask them to take part in an interview. Participants will be contacted up to three times if no response.

Clinicians will be identified from the 11 practices in the nested pilot trial by the relevant practice manager. We will ask the practice manager to identify 2 GPs in their practice who are able to take part in an interview. We will purposely sample GPs from the 16 identified to select GPs with variation in years of experience (as reported by the practice manager), we will seek to interview 10 GPs from practices in the nested pilot trial. For the main trial, we will identify practices which vary in recruitment of patients to the trial, patient list size and geography (urban/rural). We will ask practice managers in selected practices to identify one healthcare professional for an interview. We may also invite healthcare professionals from secondary care settings who have been involved in the trial and who have supported patients who have attended for PAAP. Approximately 15-25 healthcare professionals will be interviewed at the end of recruitment to the main trial. Interviews will be carried out by telephone by an experienced qualitative researcher who is part of the trial team. Oral consent will be obtained prior to interview. Interviews will follow a semi-structured design to ensure that key questions are asked to all participants but to allow flexibility for follow up questions. Participants will be encouraged to talk about any topics which are of importance to them in relation to the research aims.

Given the COVID-19 pandemic, we will also carry out additional interviews and/or focus groups prior to the main trial to explore patients' views on attending health services during the pandemic (when government guidance allows). We will identify those patients from the nested pilot study who consented to be contacted for interview on their initial consent form. These patients will be contacted by telephone by a member of the research team to invite them. Any patients who have already taken part in a previous interview during the nested pilot study will not be invited again. Patients will be invited to participate in a telephone or online (e.g. Microsoft Teams) focus group or one-on-one interview. Questions will explore patients' experience of taking part in ALABAMA and thoughts on attending health care services during the COVID pandemic, willingness to use protective measures and views on ability to travel to hospital. We will seek to include approximately 8 patients, from PAAP arm, in addition to those taking part in interviews on the nested pilot study.

7.11. Discontinuation/Withdrawal of Participants from Trial

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)

- Significant protocol deviation
- Withdrawal of Consent

The reason for withdrawal will be recorded in the CRF.

Participants randomised to the PAAP arm but who do not attend penicillin allergy testing will continue to be followed up and will be analysed as per the PAAP arm unless consent is withdrawn.

Participants who withdraw themselves will have no further data collected but data already collected will be used in the intention to treat analysis except when participants specifically withdraw consent for this.

If a participant is found to be ineligible after they have been randomised, they will be removed from the trial. Their data will not be removed from the database.

7.12 Implications for Trial Delivery During COVID-19 Pandemic

During the COVID-19 pandemic we will adhere to local NHS Trust protocols for the treatment of outpatients across the participating hospitals. Trial-specific working instructions will be regularly updated to comply with local NHS Trust guidelines in order to maintain participant safety at all times during the COVID-19 pandemic.

7.13 Definition of End of Trial

The end of trial is defined as the date of last data capture for the last participant.

8. STOP / GO CRITERIA AND PROCESS

8.1. Criteria

The criteria for the stop / go from the nested pilot to the main trial is:

- Recruitment – has the target been achieved or appropriate process modifications implemented so rate is adequate?
- Early adverse event rate after PAAP exposure – compared to the anticipated rate. This will not be quantified for the stop / go criteria but will be assessed qualitatively.

The following questions will also be reviewed at the end of the nested pilot study:

- Operational confidence:
  - Is rate of throughput in specialist immunology clinic acceptable?
  - Are penicillin allergy test results delivered to GP appropriately?
  - Do patients in the test group have their records updated with penicillin allergy test results?
  - In those with a negative test result, does their changed penicillin allergy status create an appropriate alert to inform consideration of penicillin?
  - Does the electronic patient follow up report show that a trial participant has been prescribed an antibiotic?
- Acceptability and feasibility – do patients/clinicians report that PAAP pathway content and delivery is acceptable to them and feasible for wider use?

8.2. Decision Process

Once 96 participants have been recruited into the nested pilot trial recruitment will be paused. All these participants will be followed up as described above. Once they have all 4 months of follow up an analysis of the feasibility outcomes will be performed and reviewed by the independent Data Monitoring Committee (DMC) who will make recommendations to the Trial Steering Committee (TSC) in consultation with the National Institute for Health Research (NIHR) who will confirm that the trial can continue to recruit again. This will be decided upon whether the stop/go criteria have been met, and / or where any criteria have not been met, whether sufficient amendments to the trial processes have been made that they feel the trial can continue on successfully.

All participants in the nested pilot trial will continue to be followed up for a minimum of 12 months and will also be included in the main trial sample size.

9. BEHAVIOUR CHANGE INTERVENTIONS

Intervention materials are required to support GPs and patients to carry out specific behaviours related to PAAP. These behaviours include GPs referring patients to PAAP, patients completing PAAP Stages 2 and 3, prescribing penicillin in consultations following a negative test result and patients consuming penicillin when prescribed. Intervention materials are likely to take the form of electronic and paper-based materials which can be disseminated to clinicians and patients easily and which are low cost.

Patients' intervention materials are likely to include:

1. Patient Pre-test Intervention Booklet
    - Will provide information about the test (what happens, where, with which staff), address patient concerns about attending for test (safety, effort involved and reliability) and emphasize personal relevance of test (potential personal benefits of negative test result)
    - To be sent when booked clinic appointment for PAAP stage 2 and 3.
2. Patient Post-test Intervention Booklet
    - Will address reliability of test result, consequences of test result, and provide advice on discussing test result in future consultations.
    - To be sent with test result letter.
3. Patient Intervention Card
    - Laminated, credit card-sized card which says which test patient has undertaken and confirms negative allergy result. Will confirm which penicillin the patient has been tested with and confirm patient can be prescribed penicillin antibiotics with the same risk as the general population.
    - To be sent with test result letter.

Clinician intervention materials are likely to include:

1. Information pack
    - PDF document which will inform prescribers about what the test involves and the reliability of results, the benefits of testing for individual patients and the public, and how to select and refer patients for testing.
    - Given to all prescribing staff when practices sign up to trial.

2. Electronic health record pop up
    - Pop up on computer which reminds/tells clinician that patient has had negative results to penicillin allergy test and that their allergy status has been removed. Message contains link to Information pack. Message specifies which drugs clinicians can prescribe safely.

10. SAFETY REPORTING

Safety of the trial participants is paramount. Consequently, PAAP testing will be performed in a hospital clinic set up for allergy testing to mitigate any risk of dealing safely and swiftly with anaphylaxis or other serious reaction to the oral challenge test, where suitably qualified and trained personnel and equipment are at hand. Access details to out-of-hours contact will be given to all participants as is the standard of care for all penicillin-allergy assessments to enable appropriate management of problems that might develop after the participants return home.

10.1. Adverse Events

10.1.1 Adverse events due to Penicillin Allergy Testing:

Telephone calls by the research team at the following time-points will collect information on adverse events (AEs) associated with the penicillin allergy test (skin test and/or oral challenge test): 4 – 6 days and 28 – 30 days after-penicillin allergy testing.

The specific events (expected reactions) that are captured by our post-penicillin allergy testing questionnaires are listed below:

- Red rash (affecting a large part of the body, no blistering, non-itchy)
- Red rash (affecting a part of the body, no blistering, non-itchy)
- Rash with blistering
- Urticaria (red blotchy/itchy rash)
- Rash (no details known)
- Swelling of the face
- Swelling of the tongue
- Swelling of the hands
- Swelling of other parts of the body
- Difficulty breathing
- Sneezing
- Nausea
- Vomiting
- Abdominal discomfort or diarrhoea
- Collapse – with loss of consciousness
- Thrush

These events are recorded and reported routinely to DMEC without further action.

10.1.2 Post-Antibiotic Prescriptions in primary care:

Adverse events occurring up to 28 days after an antibiotic prescription from their general practitioner for any pre-defined infections listed in Appendix G will be captured through telephone calls by the research team at the following time points; 2 – 4 days and 28 – 30 days after the start of an antibiotic prescription.

We will capture any adverse event that results in a change of antibiotic prescription through the safety review telephone calls and/or remote electronic health record review.

The specific events (expected reactions) that need to be recorded post antibiotic prescriptions are listed below:

- Red rash (affecting a large part of the body, no blistering, non-itchy)
- Red rash (affecting a part of the body, no blistering, non-itchy)
- Rash with blistering
- Urticaria (red blotchy/itchy rash)
- Rash (no details known)
- Swelling of the face
- Swelling of the tongue
- Swelling of the hands
- Swelling of other parts of the body
- Difficulty breathing
- Sneezing
- Nausea
- Vomiting
- Abdominal discomfort or diarrhoea
- Collapse – with loss of consciousness
- Thrush

Adverse events occurring up to 28 days after an antibiotic prescription for any pre-defined infections listed in Appendix G will be captured through telephone calls by the research team at the following time points; 2 – 4 days post antibiotic episode; and 28 – 30 days post antibiotic episode.

We will capture any adverse event that results in a change of antibiotic prescription through the safety review telephone calls and/or remote electronic health record review.

10.2. Definition of Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

- Anaphylaxis to an antibiotic will be considered an SAE as part of the ALABAMA trial.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Any SAEs identified during the ALABAMA trial need to be assessed for their relatedness to:

1. Penicillin Allergy Assessment (PAA)
2. An antibiotic prescription* for any of the pre-defined infections listed in Appendix G.

*Because patients may have more than one antibiotic prescription during the ALABAMA trial, the relatedness of SAEs should be assessed in relation to their most recent antibiotic prescription for any pre-defined infections listed in Appendix G.

10.3. Procedures for Recording Serious Adverse Events

Telephone calls by the research team at the following time-points will collect information on hospitalisation and anaphylaxis: 4 – 6 days post-PAAP; 28 – 30 days post-PAAP; 2 – 4 days post antibiotic episode; and 28 – 30 days post antibiotic episode for any pre-defined infections listed in Appendix G. Participants in the nested pilot will also be called monthly for 4 months to assess any safety events. If not captured through the telephone calls, we will collect any other SAE by SystmOne reports, remote electronic health record review, HES and mortality data, at month 4 as part of the nested pilot and month 12 for the main trial.

10.4. Reporting Procedures for Serious Adverse Events

All SAEs will be reported to medical supervisors for review and assessment. The Sponsor will also be notified of all SAEs on a quarterly line reporting basis.

An SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the trial where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND QUALITATIVE ANALYSIS

11.1. Description of Statistical Methods

Analyses will be described in detail in a Statistical Analysis Plan (SAP) drafted by a Trial Statistician and signed off by the CI and Lead/senior statistician. All analyses will be conducted in accordance with Oxford Primary Care CTU SOPs. Our main planned analyses are summarised below.

In accordance with CONSORT guidelines, we will record and report participant flow. Recruitment, drop-out, and completeness of interventions will be analysed descriptively. The primary analysis population will include all participants for whom data are available and will be analysed according to the groups they are randomly allocated to. Baseline variables will be presented by randomised group using frequencies (with percentages) for binary and categorical variables, and means (and standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor

confidence intervals for differences between groups on any baseline variables. There will be no planned interim analysis for efficacy.

The primary outcome, i.e. penicillin prescribing, will be analysed using a mixed effect generalised linear model (MGLM), adjusting for differential follow-up as appropriate. GP sites will be included in the model as a random effect and the other minimisation factors will be treated as fixed effects. Similar approaches will be used for the secondary outcomes. For data where distributional assumptions are violated, suitable non-parametric methods will be used. Appropriate regression models (such as Poisson regression, Hurdle models etc.) will be used for the analysis of count outcomes. Models will adjust for relevant baseline covariates and minimisation factors as appropriate. Where there is a paucity of data, outcomes will be analysed using univariate tests or presented descriptively.

For the nested pilot study, the analysis of all the feasibility outcomes and the analysis of patients questionnaires will be descriptive, focusing on determining the overall feasibility parameters to inform the main trial.

11.2. The Number of Participants

The primary outcome, was initially treatment response failure defined as the percentage of re-prescription of an alternative antimicrobial within 28 days of an index prescription. A total sample size between 1592 and 2090 participants provided 80-90% power to detect a clinically important absolute difference of 7.9% in re-prescription rate at one year between groups (i.e. reducing from 19.8% in the control group to 11.9% in the PAAP group) at 5% level of significance (2-sided). The sample size had been adjusted assuming 50% of participants will require at least one prescription within 1 year from randomisation and allowing for 10% dropout. Participants are classed as enrolled at the point of randomisation.

We have since changed the primary outcome to 'effects of PAAP on penicillin prescribing', defined as 'The proportion participants who receive prescriptions for a penicillin attending for predefined conditions where a penicillin is the first-line recommended antibiotic (APPENDIX G) during the course of routine primary care up to 12 months post randomisation. A total sample size of 848 (i.e. 424 per group) is required to provide a 90% power to detect an increase in the proportion of penicillin prescription from 4% (Usual Care) to 14% (PAAP) over the year after randomisation at 5% level of significance (2-sided) and 10% attrition. The sample size has been adjusted assuming 50% of participants will require at least one prescription within 1 year from randomisation. At 80% power, the sample size required is 656 (i.e. 328 per group). The table below also provides the sample size required if not all participants have reached 12 months follow-up.

Power	% Difference	Total sample size (all reached 12 months follow-up)	Total sample size (80% reached 12 months follow-up)	Total sample size (90% reached 12 months follow-up)
80%	10%	656	820	729
	15%	372	465	413
90%	10%	848	1060	942
	15%	472	590	524

Results from our recent analysis, using data extracted from the SystmOne database, suggested that there were an average of 110 patients per average practice size of 6000 who fulfilled our inclusion criteria.

(1) Adults (over 18 years)

(2) Pen-allergy in electronic health records

(3) And in receipt of a penicillin, cephalosporin, tetracycline, quinolone or macrolide class antimicrobial in the previous 24 months.

Not all patients will have an eligible antibiotic prescription for an infective episode during the follow up period, and not all episodes will generate analysable data. We have allowed for 50% patients not contributing any data to the primary outcome and that some patients will contribute more than one episode. The first 96 participants recruited will comprise the sample for the nested pilot trial.

11.3. The Level of Statistical Significance

The level of significance will be 5% (2-sided).

11.4. Criteria for the Termination of the Trial

It is not anticipated that the trial will be terminated unless on the advice of the DMC in the case of a series of Suspected Unexpected Serious Adverse Reactions (SUSARs). No statistical interim analysis is planned for the main trial.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data

Missing data will be reported, with reasons where available, and the missing data mechanism explored. Sensitivity analysis using imputation methods, such as multiple imputation for data missing at random mechanism, will be considered.

11.6. Inclusion in Analysis

The primary analysis population will include all randomised patients in the treatment arm they were assigned regardless of treatment received. All data will be included in the analysis as far as possible, though there will inevitably be the problem of missing data due to withdrawal, loss to follow-up, or non-response questionnaire items. For the “as treated” (AT) analysis population, all participants who were allocated to PAAP and also have completed the test will be included in the analysis. Those participants who failed to complete the test will be included in the usual care arm for “as treated” analysis. Participants withdrawn for post-randomisation ineligibility will be excluded from all outcome analyses.

11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

We do not anticipate any deviation from the statistical plan outlined above. However, provision for alternative methods and changes to analyses will be included in the Statistical Analysis plan as specified in the PC-CTU’s SOP “Statistical Analysis Plan”.

11.8. Qualitative Analysis

Qualitative data, from interviews with healthcare professionals and patients, will be analysed using thematic analysis taking an inductive approach [20 21]. NVivo software will be used to assist with the

organisation of data. A thematic framework will be used to chart data across all interviews and will aid comparisons between participants.

11.9. Cost-effectiveness Analysis

Health related Quality of life (HRQoL) will be assessed in all randomised patients. In addition, resource use and cost-effectiveness will be assessed within the trial.

11.9.1 Quality of life and data collection

Quality of life (QoL) will be assessed via the following validated research questionnaire:

• EQ-5D-5L (EuroQol)[22]

QoL will be collected from patients over the phone by research staff at the following time points (unless otherwise stated), regardless of whether the patient is receiving the PAAP intervention or not:

• Baseline, pre-randomisation (by telephone)

• 12 months post PAT (+/- 2 weeks) (by telephone)

When trial relevant antibiotics are prescribed, patients will be contacted at 2-4 and 28-30 days post antibiotic treatment commencing (by telephone) to remind them to complete their diary and EQ5D-5L will also be collected.

11.9.2 Within trial cost-effectiveness analysis

The within trial economic evaluation will estimate the incremental cost per QALY for PAAP intervention versus usual care from the perspective of the NHS. The analyses will use trial data collected up to 12 months follow up post PAT.

The trial economic evaluation will evaluate the cost per unit of gain in primary outcome measure. However, as economic evaluations are designed to inform resource allocation decisions, evaluations will also be produced using overall survival and quality adjusted life years (QALYs) outcome measures. The estimation of QALYs requires the production of utility weights at baseline and twelve months for each individual observed in the trial population. We will use the EQ-5D-5L (EuroQol) instrument for this purpose[22].

NHS resource use associated with each intervention will be collected. The resource use and costs relating to the delivery of the PAAP intervention and current methods of pen-allergy testing as experienced by usual care arm patient participants will be collected; the former, as part of the trial, and the latter using unit cost data from published costing studies. Follow up will provide details of the number/duration of appointments and the specialty of professionals involved. Data will be collected via:

(i) SystmOne (primary/community care)

(ii) Linked HES (secondary care: inpatient, A&E, outpatient and critical care datasets) and ONS mortality data

(iii) The linked HES data will facilitate a directed search for prescribing data in secondary care, from electronic prescribing systems or by the trial team through hand searching patient records (if available/accessible) for patients receiving secondary care.

Unit costs of medication will be obtained from the Prescription Cost Analysis database, for primary care prescriptions, and from the eMIT database or (for medications not found in this database) BNF list prices, for prescriptions in secondary care. Unit costs of primary or community services will be obtained from Personal Social Services Research Unit, whilst NHR Reference costs will be used to value secondary care services. Costs and outcomes will not be discounted at 3.5% due to the single year timeframe of the trial, in line with current recommendations.

Incremental cost effectiveness ratios (ICER) will be measured in terms of cost per QALY gained with PAAP over usual care. Parameter uncertainty will be quantified using non-parametric bootstrapping techniques. Outputs will be presented as ICERs, cost effectiveness acceptability curves and expected net benefit. In this analysis, the sampling distribution of the ICER of PAAP will be used to estimate its likelihood of being below the NICE threshold of £20,000 per QALY that defines cost-effectiveness. The impact of missing data will be examined using imputation methods. Sensitivity analyses will consider key cost drivers and factors that might affect the outcomes measured to explore uncertainty in the conclusions drawn.

11.9.3 Model based extrapolation beyond the 12 month-trial endpoint

A Markov model will be developed to model the differences in costs and QALYs that are likely to accrue beyond the period of trial follow-up. The model will be informed by a review of the health economic and epidemiological literature of incidence of bacterial infections in patient cohorts drawn from the same reference patient population as that of the ALABAMA trial. The model will be based on the rate of amended primary care patient records at the end of ALABAMA follow-up to simulate the subsequent transition of members of the trial patient cohort between susceptible and infectious states up to 5 years after randomisation.

For informing the development of the model, we are conducting a systematic search of the health economic literature to be designed by a senior Information Specialist at the Leeds Academic Unit of Health Economics in consultation with the health economics lead and a senior modeller appointed to work in this project. The model will also be populated with data from large observational studies of the NHS cost and patient record implications of penicillin allergy labels and de-labelling, conducted by ALABAMA project co-investigators or collaborators.

The analysis will explore accounting for the public health and economic impact of PAAP on antimicrobial resistance, based on published mathematical models of resistance emergence and development to antibiotics as a function their use in the population. Costs and QALYs will be discounted at an annual rate of 3.5% from the second year onwards.

Probabilistic sensitivity analysis will be conducted to account for sampling uncertainty in the epidemiological, costs and utility model parameters. Results will be presented in terms of the probability of PAAP being cost-effective after 5 years.

11.9.4 Value of Information Analysis

Based on the probabilistic Markov model described in 11.9.3, the value of conducting further research in key uncertain outcomes will be determined using the Expected Value of Perfect Partial Information. This analysis will determine whether the costs of conducting further research on uncertain parameters is

justified by the expected costs associated with the risk of making the wrong decision on the basis of the state of the evidence base at the end of ALABAMA.

12. DATA MANAGEMENT

12.1. Source Data

Source documents are where data is first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, primary care and hospital records (e.g. medical history, antibiotic use, outcomes), diaries and telephone questionnaires.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, participants will be anonymised and will be referred to by their trial participant number/code only, not by name.

Participant diaries will either be recorded on paper CRFs or directly into the database, REDCap. Telephone questionnaires will either be recorded on paper CRFs or directly into the database, OpenClinica. The SystmOne report will be used as a stand-alone report which will be amalgamated with the data captured in OpenClinica for the primary and secondary care notes review.

The primary outcome data is being collected by three data collection methods: SystmOne report, telephone questionnaires, and notes review (primary & secondary care). Further information on this process will be described in the statistical analysis plan.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the trial to ensure compliance with regulations.

Delegated members of the trial team will have access to participants' medical records using the SystmOne electronic health record system (TPP) and through manual notes review. Consent will be obtained prior to access.

12.3. Data Recording and Record Keeping

Data Management will be performed in accordance with PC-CTU Data Management SOPs. Trial specific procedures will be outlined in a Data Management Plan to ensure that high quality data are produced for statistical analysis. The DMP is reviewed and signed by all applicable parties including the Trial Manager and the Trial Statistician prior to the first patient being enrolled.

Sentry is an online secure data entry system developed in-house at PC-CTU and hosted at Oxford. It is designed to collect sensitive data, such as participant and Trial Partner contact details, and securely retain them separate form a trial's clinical data. Sentry is accessed via a secure HTTPS connection and all stored sensitive data is encrypted at rest to AES-256 standards. Participant and Trial Partner data will be kept and

stored securely until the study has finished. Sentry will also be used for sites to complete the eligibility CRF and informed consent forms for patients at their site.

All participants will be consented either online or by using pre-printed paper consent forms. *Sortition* will be used for randomisation. *Sortition* is a secure, web-based, system developed in conjunction with the clinical trials unit. The OpenClinica system will incorporate data entry and validation rules to reduce data entry errors, and management functions to facilitate auditing and data quality assurance. Data protection requirements will be embedded into the design of the web-based system and enforced by best practice trial management procedures. The Clinical Data Manager will oversee the process of electronic data validation and manual listings, sending out Data Clarification Forms (DCFs) when required and following these up until the queries are resolved.

Once the last participant is enrolled, prior to database lock a dataset review will be undertaken by the Clinical Data Manager and Trial Statistician. All critical data items are 100% checked against original Source Data Documents to ensure accuracy. An error rate is established across all fields to ensure a consistently accurate dataset.

Participants' contact information will be collected in paper form and sent to the trial team. The contact details will be stored by the trial team separately from all other trial data.

The trial team will preserve the confidentiality of all data obtained which are to be kept by the ALABAMA trial team in compliance with the Data Protection Act (DPA) 2018 and PC-CTU Data Management SOP, this includes data of trial participants.

At the conclusion of the trial and after the database has been locked, all essential documents will be archived in accordance with the PC-CTU's Archiving SOPs. The Chief Investigator is responsible for authorising retrieval and disposal of archived material.

12.4. SystmOne and ALABAMA Unit

SystmOne is a clinical system utilising a 'one patient, one record' model of healthcare. Using SystmOne, clinicians can access a single source of information, detailing a patient's contact with the health service across a lifetime. The GP's recruiting into ALABAMA will have SystmOne set up as part of their routine practice. TPP, the healthcare technology company that have developed SystmOne have also developed a system by which delegated members of the ALABAMA trial team can access consented participants medical records using an 'ALABAMA unit' with their SystmOne clinical health records. Participant's clinical health records cannot be altered by the trial team but selected information, alerts, tasks and data reports can be set-up, viewed and/or downloaded using this interface as required and pre-specified for the trial.

A number of trial processes will rely on this system but as this is a novel technology the nested pilot trial will explore collection of the required data and activation of the required alerts in parallel with traditional data collection methods such as notes reviews and manual tracking of trial procedures and alerts.

12.5. Quality Assurance Procedures

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU standard operating procedures. The PC-CTU has in place procedures for assessing the risk management for trials which will outline the monitoring required. The investigators and trial related site staff will receive appropriate training in good clinical practice and trial procedures. Data will be evaluated

for compliance with the protocol, GCP and the applicable regulatory requirements. The PC-CTU trial management group will be responsible for monitoring all aspects of the trials conduct and progress and will ensure that the protocol is adhered to and that appropriate action is taken to safeguard participants and the quality of the trial itself. The TMG will be comprised of individuals responsible for the day to day management (e.g. the CI, trial manager, statistician, data manager) and will meet regularly throughout the course of the trial.

A Data Monitoring Committee (DMC), Trial Management Group (TMG) and Trial Steering Committee (TSC) will be appointed in line with standard CTU procedures. The responsibilities of each group are as follows:

- DMC- to review the data at each interim analysis, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety and wellbeing of the trial participants. They will make recommendations to the TSC about how the trial is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial.
- TMG- is responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to.
- TSC- to provide overall supervision of the trial on behalf of the Sponsor and the Funder to ensure that it is being conducted in accordance with GCP. The TSC will review the trial regularly, agree any amendments and provide advice on all aspects of the trial.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the trial, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

NHS Digital will be used to inform the trial of those participants who die or move away from the area and HES data. We will also request permission for their electronic records to be reviewed using the SystmOne ALABAMA unit to gather data on any relevant health conditions, investigations, treatments, hospitalisations and mortality over a 10 year period. Patients themselves will not be asked to attend any further trial visits.

In order to get information from NHS digital, we will share identifiable data (for instance name, date of birth and NHS number) in a secure manner (including encryption during data transfer). For future ethically approved studies the anonymised data will be linked between studies using the participant ID. Anonymity of data will be maintained at all times by using the unique participant ID and which will be the only link between personal identifiers and the data itself.

13.6. Expenses and Benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided or local pragmatic arrangements as appropriate.

14. FINANCE AND INSURANCE

14.1. Funding

This trial is funded by National Institute for Health research (NIHR).

14.2. Insurance

Where the University is acting as Sponsor, the University has in force a Public and Products Liability policy which provides cover for claims for "negligent harm" and the activities of this trial are included within that coverage subject to the terms, conditions and exceptions of the policy. NHS indemnity operates in respect of the clinical treatment that is provided.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the trial. Authors will acknowledge that the trial was funded by the NIHR. Authorship will be determined by the CIs in accordance with the ALABAMA Publication Policy developed with the Trial Management Group in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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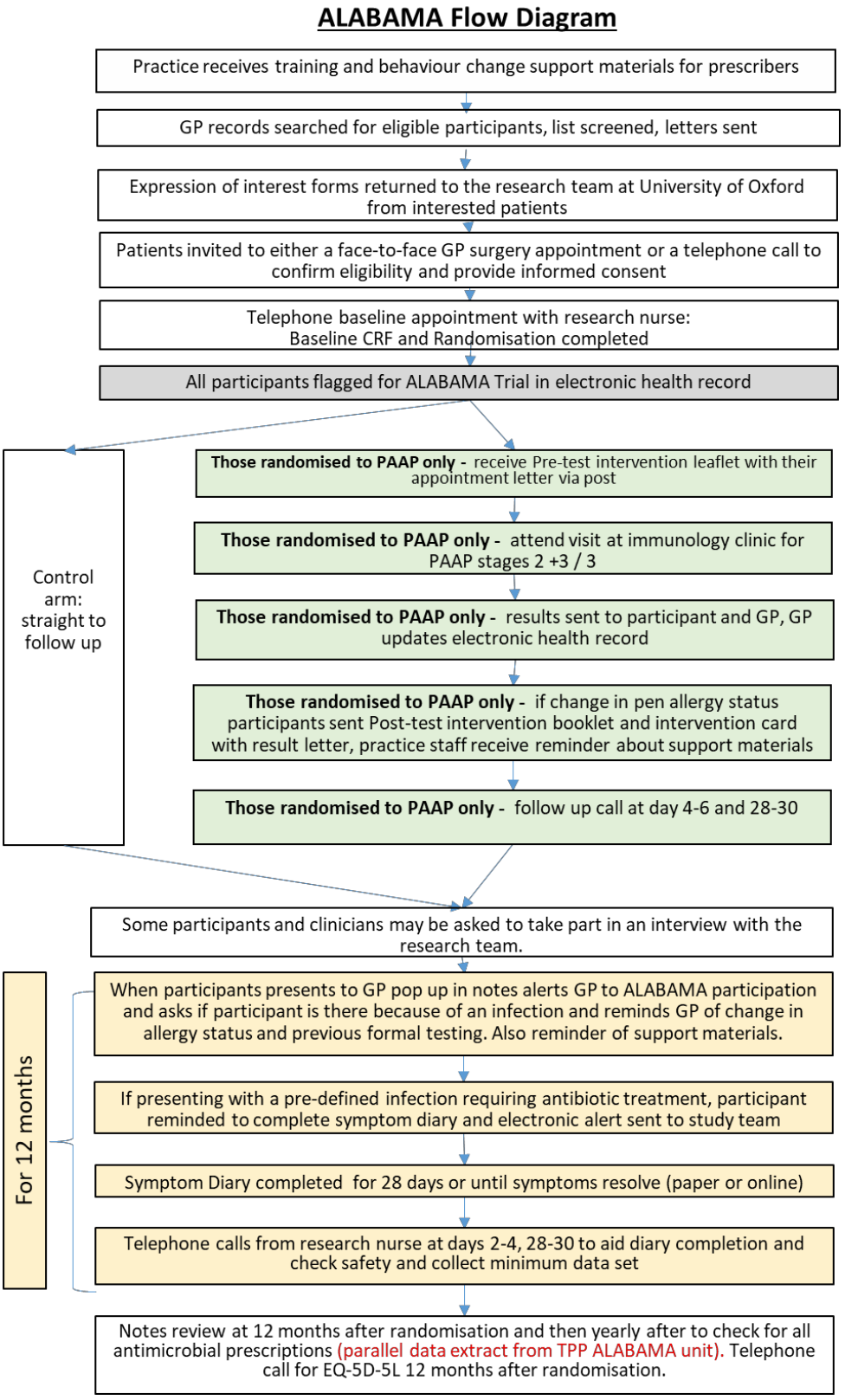
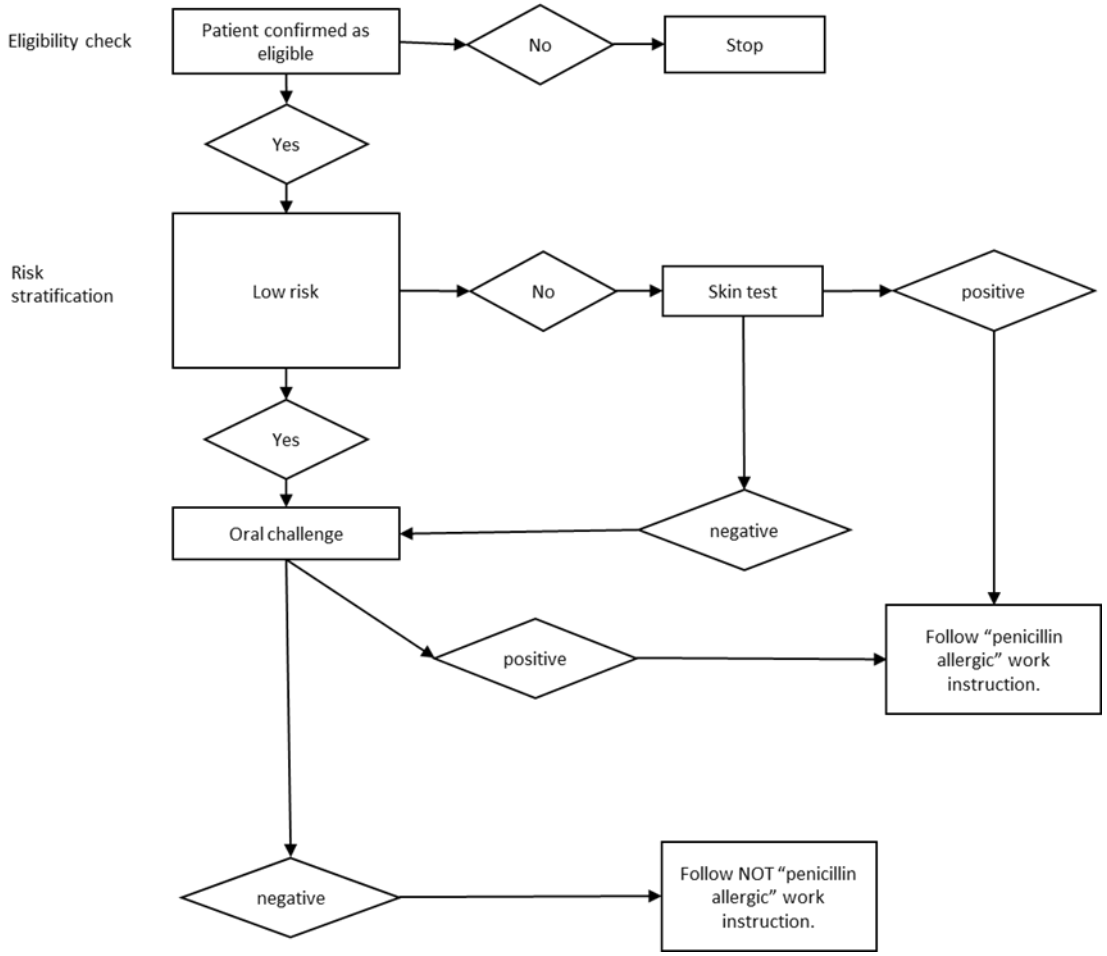
APPENDIX A: TRIAL FLOW CHART



17. APPENDIX B: PAAP FLOW DIAGRAM

Testing strategy flow chart



18. APPENDIX C: ALABAMA Trial Intervention -Penicillin Allergy Assessment Pathway (PAAP)

Summary of operations:

Stage-1 PAAP in Primary Care – Clinical History. Screening, questionnaire and antimicrobial history will be undertaken in primary care

Stage-2 Skin Test(ST) in hospital clinic (this may not be needed for all participants)

Stage 3 Oral Challenge Test (OCT) in hospital clinic

Testing will involve half a day in clinic and then a three-day post clinic course of oral antimicrobial therapy, without a reaction

Background

Assessment of patients with penicillin allergy in specialist clinics is an existing service provided within the NHS. Testing involves:

1) clinical evaluation (allergy and antimicrobial history);
2) skin testing (not needed for all patients);
3) oral challenge test (OCT) (sometimes also called oral provocation tests).

The allergy history is important to determine if the allergy history is spurious, of uncertain risk or high risk of true penicillin allergy.[7] Skin testing and oral challenge tests may follow.
In many immunology/allergy clinics penicillin allergy testing is undertaken over at least two clinic visits; one to undertake history taking and skin prick testing the others to assess reactions and undertake oral challenge.
The ALABAMA trial proposal is different from standard NHS practice in two ways:
1) we aim to make the allergy testing pathway more efficient but simplifying the process, undertaking initial elements in the community and developing a "one stop shop" single clinic visit for specialist assessment; 2) pre-emptive testing will be undertaken in patients with a high likelihood of needing antimicrobial therapy, rather than in the acute setting or soon after a reaction. Evaluation of this pragmatic approach to allergy testing would facilitate wider testing within the NHS, should this become appropriate. Note: The proposed trial testing will take place in a hospital clinic set up for allergy testing by appropriately trained staff in an NHS setting.
It is important to note that pre-emptive allergy testing as outlined in the ALABAMA PAAP intervention is different from testing a patient who has an absolute need for penicillin to treat a life- threatening infection. The risk benefit analysis is different in these two situations and a more cautious approach has been taken in the ALABAMA PAAP than might be taken in the alternative scenario.

Stage 1 PAAP in primary care – Clinical history

The allergy history is key element of the penicillin allergy assessment pathway.[1] Once patients who fulfil the inclusion criteria have been identified by screening eHR their suitability for the trial, i.e. identifying patient who fulfil exclusion criteria will be assessed by their general practitioner or their deputy.

For the purposes of this trial (which needs to be pragmatic for the findings to be applicable to routine NHS practice), a convincing history of an immediate, (within 1 hour) anaphylactic reaction or severe/blistering skin rash to a penicillin will be taken to be a genuine allergy and an exclusion criterion for further testing. This is the practice in the Leeds Immunology Department. We acknowledge that not all patients with a history of anaphylaxis to a penicillin have had a true penicillin-mediated anaphylaxis, but in this context, safety is a priority – so such patients will be excluded from further testing and from further analysis.[1]

Risks and safety

This assessment involves taking a clinical history from the patient. The only risk associated with this element of the process is if the interviewer/interviewee misunderstands a question/answer and takes the wrong path through the PAAP. This would be addressed by ensuring effective information exchange through the qualitative interview and pilot stages, and the research nurse checking the clinical history prior to skin testing.

Stage 2 Skin testing in hospital clinic set up for allergy testing

Skin testing is an established tool in the assessment of penicillin allergy and will be used to select some patients for oral challenge.[3] Both skin prick testing and intradermal testing are required: Of 998 skin tested patients, over an eight year period, 147 (14.7%) had skin test positive results, only 30 (3%) of which were skin prick test positive.[2] Testing in advance of need has been described previously and 568 such patients with negative skin prick tests were followed up to investigate those who went on to receive at least one course of penicillin; there were four reported anaphylactic reactions.[4] On further investigation none of these reactions occurred within one hour of antimicrobial ingestion; none of these patients had systemic symptoms of shortness of breath, faintness, or decreased blood pressure; none received adrenaline or intravenous fluids, and all resolved with either no therapy or with antihistamine and/or steroid therapy.[4] Three of the four patients had repeated penicillin skin tests, and all were negative.[4] None of the adverse reactions identified in this trial resulted in emergency department treatment and/or hospitalization. The majority of skin test negative patients will be given an oral challenge. The positive predictive value of skin testing in the assessment of risk of an allergic reaction to penicillin is not known because patients who have a history consistent with a type I reaction to penicillin who subsequently react to skin testing do not usually proceed to oral penicillin challenge.[1] When penicillin treatment has occurred in this setting, reaction rates are high (50-70%).[1]

Risks and safety

Skin prick testing is generally safe and systemic reactions following testing are rare.[2] For example, five patients (0.5%) had systemic reactions in one eight year series including 998 skin tests.[2] To be prudent, skin prick testing will take place in a specialist unit with facilities to deal with any potential severe allergic reactions. Fatalities during skin prick testing have been reported but are very rare; a historical review of fatalities following skin testing (not necessarily pen-allergy testing) between 1945 and 1987 found 5 cases, not all of which could be clearly attributed to the testing.[5]

Stage-3 Oral challenge test in hospital clinic.

Oral challenge tests (OCT, also called drug provocation tests) are needed in patients with a negative skin test because false negative skin tests can occur.[6]
Ideally, we would opt to challenge the patient with the same type of penicillin to which the patient reacted. Unfortunately, this information is frequently lacking, especially in historic cases, where reaction might have occurred many years ago. Since amoxicillin is now the most commonly prescribed antimicrobial of the penicillin class and the most frequent cause of allergic reactions, in cases where the culprit is unknown we will challenge with amoxicillin. If the patient does not suffer a reaction after this initial challenge they will be given a 3-day course of antimicrobial to take at home and will be followed

up by telephone to check for delayed early reactions. If there is no reaction to the oral challenge, patients can then be treated with an oral or parenteral penicillin.

Risks and safety

Systemic reactions to a challenge in penicillin skin-prick negative patients are uncommon but do occur. There is considerable variation in the published literature 0.75-8.4% of skin prick negative patients who were challenged had possible IgE mediated reactions.[6, 7] Among 580 orally challenged patients with a history of non-serious skin reactions to penicillin, 14 had reactions, 11 of which were early and 3 delayed.[8] A reaction was more likely if the allergy report was within 15 years. In the 280 patients with a reaction within the last 15 years an original reaction within one day of the dose was associated with greater likelihood of reaction to challenge 7/64 (11%).[8] Several studies have used penicillin oral challenge in patients with a positive histories of penicillin allergy but negative skin test results, and the results are consistent: the vast majority of patients tolerated the challenge and those who did not experienced only urticarial or mild skin reactions.[1] When 6739 patients with a penicillin allergy history and negative skin test results were given penicillin, only 101 (1.49%) developed an IgE-mediated reaction and 43 (0.63%) developed a delayed reaction.[1] Penicillin anaphylactic shock was not reported in subjects with negative skin test results who received a penicillin challenge. Eligible patients with a penicillin allergy label who have negative skin test results will receive an oral penicillin challenge.

An abbreviated incremental challenge or a single dose challenge will be used depending on a risk assessment, based on that advised in UK guidelines.[3]

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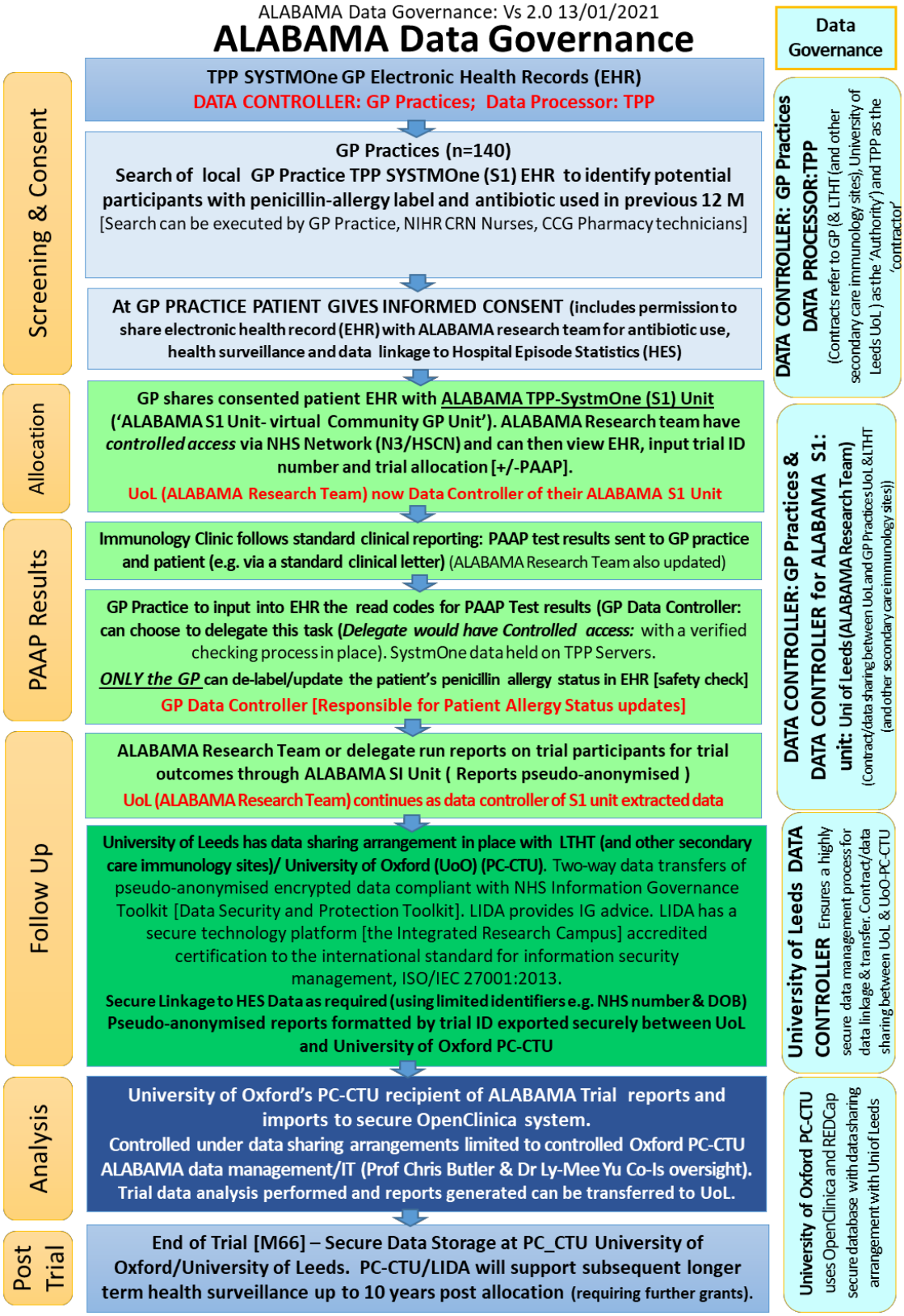
19. APPENDIX D: SCHEDULE OF TRIAL PROCEDURES

	Electronic identification of suitable participants by GP or a delegated member of staff	Eligibility and consent appointment with GP or a delegated member of staff	Baseline appointment by Research Team (telephone)	Allergy testing at hospital clinic visit for Penicillin allergy tests (PAAP)	4-6 days post PAAP Research Team calls the participant	28-30 days post PAAP Research Team calls the participant	2 month post-baseline FU – RN calls participant	3 month post-baseline FU - RN calls participant	4 month post-baseline FU –RN calls participant	GP visit + antibiotic episode of trial relevance	2-4 days Post antibiotic episode - Research Team call	28-30 days Post antibiotic episode – Research Team call	12 month post randomisation phone call by Research Team
							1. Nested pilot only						
Eligibility	x	x	x										
Consent		x											
Medical History and demographics			x										
Penicillin allergy history			x										
Allergy belief			x			x					x		
EQ5D5L			x								x	x	x
Randomisation			x										
Skin Testing				x									
Oral Challenge Test				x	x								?
safety:				x	x	x	x	x	x		x	x	
Participant daily diary (28 days)										x	x (reminder		
Primary outcome questionnaire												x	
Notes review									x				x

20. APPENDIX E: Diagram of data flow from SystmOne to the OpenClinica database



21. APPENDIX F: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	09/05/2019	Dr Jonathan Sandoe Mina Davoudianfar	Amended the documents below: • Reply slip • Consent Form • Clinician Interviews Consent Form: • Clinician Interviews Information Leaflet • Patient Interviews Consent Form • Patient Interviews Information leaflet • Protocol • Participant Information Sheet • Invitation Letter • Baseline Questionnaire: • Post PAAP (Day 4-6) Questionnaire: • Pot PAAP (Day 28-30) Questionnaire: • Month 2 FU Questionnaire: • Month 3 FU Questionnaire: • Month 4 FU Questionnaire: New documents created following TMG discussion: • Symptom Diary Email Reminder Day 1 • Symptom Diary Email Reminder Day 2 onwards • Online Symptom Diary Instruction • Feasibility FU form (Month 1)
2	2.0	29/07/2019	Dr Jonathan Sandoe Mina Davoudianfar	Amendments to the following documents: • Baseline Questionnaire

				• Post PAAP Questionnaire (Day 4-6) • Post PAAP Questionnaire (Day 28-30) • Post Antibiotic (Day 2-4) Questionnaire • Post Antibiotic (Day 28-30) Questionnaire • 1 Month FU Questionnaire (nested pilot) • 2 Month FU Questionnaire (nested pilot) • 3 Month FU Questionnaire (nested pilot) • 4 Month FU Questionnaire (nested pilot)
3	2.0	03/09/2019	Dr Jonathan Sandoe Mina Davoudianfar	Creation of new documents below: • ALABAMA PAAP Appointment Letter • ALABAMA Patient Negative Results Letter • 2.ALABAMA Patient Positive Results Letter • A.ALABAMA GP OCT Negative Results Letter • B. ALABAMA GP SPT OCT Negative Results Letter • C. ALABAMA GP SPT Positive Results Letter • D. ALABAMA GP SPT Negative OCT Positive Results Letter
4	3.0	10/01/2020	Dr Jonathan Sandoe Mina Davoudianfar	Amendments to the following documents: • Protocol • Reply Slip • Invitation letter • Clinician Interviews Verbal Consent Form • Clinician Interviews Invitation Letter • Patient Interviews Verbal Consent Form

				• Patient Interviews Invitation Letter PAAP Arm • Text Message Script • Patient Information Sheet Creation of new documents below: • Non-Responders Letter • GP Practice Poster • Pharmacy Poster • GP OCT Positive Results Letter • Patient Interviews Invitation Letter Control Arm • Patients Interviews PIL Control Arm • Verbal Consent Form • Follow up Phone Call Topic Guide
5	4.0	05/10/2020	Dr Jonathan Sandoe Mina Davoudianfar	Amendments to the following document: • Protocol Creation of new documents below: • COVID IFG Topic Guide • COVID Interviews Focus Groups ICF • COVID Interviews Focus Groups PIL
6	5.0	20/01/2021	Dr Jonathan Sandoe Mina Davoudianfar	Amendments to the following documents: • Protocol • Patient Information Sheet • Consent Form • Verbal Consent Form • Text Message Script • Invitation Letter • Non-responder Letter • GP Practice Poster • Pharmacy Poster • Reply Slip • Follow up Phone Call Topic • Symptom Diary • A. ALABAMA_GP_OCT NEG_Results Letter

				• B. ALABAMA_GP_ SPT OCT Neg_ Results Letter • C. ALABAMA_GP_ SPT Pos_ Results Letter • D. ALABAMA_GP_SPT Neg_ OCT Pos_Results • E. ALABAMA_GP_ OCT Pos_ Results Letter • Baseline Questionnaire • Post Antibiotic (Day 2-4) Questionnaire • Post Antibiotic (Day 28-30) Questionnaire • Post PAAP (Day 4-6)_Questionnaire
7	6.0	10/05/2021	Dr Jonathan Sandoe Mina Davoudianfar	• Section 11.1, (Description of Statistical methods) has been updated • Section 11.2, the number of participants is updated to increase the target number of sites from 70 to 140 and the target number of participants per practice has changed from 30 to 15-21.
8	7.0	26/11/2021	Dr Jonathan Sandoe Kelsey Armitage	• List of Investigators has been updated • Exclusion criteria has been updated • Added the option of txt message reminders to be sent to the patient if uncontactable at baseline/randomisation and to arrange PAAP appointment Amendments to the following document: • Patient Information Sheet • Patient Negative Results Letter • Verbal Consent Form Creation of new documents below:

				• Text Message Scripts_After Mail Out • Text Message Scripts_Post Consent
9	8.0	10/05/2022	Dr Jonathan Sandoe Kelsey Armitage	• Average Daily Quantity (ADQ) has been removed as a secondary outcome measure for the effects of PAAP on total antibiotic prescribing. • Sample size amended to allow for a range of between 80-90% power analysis • Updated list of antibiotics in inclusion criteria • Added the collection of basic demographics to Baseline Assessments • Clinician questionnaire removed from process evaluation • Appendix C updated to include the option of single dose challenge depending on a risk assessment.
10	9.0	10/06/2022	Dr Jonathan Sandoe Kelsey Armitage	• Updated to clarify that treatment response failure will only be collected over the year subsequent to randomisation. • Updated to reflect that the patient symptom diary will only be completed after first primary event since randomisation.

				• Section 6.3 Clarification added to exclusion criteria for pregnant and breastfeeding mothers. • Section 7.3 statement added to highlight opportunistic recruitment is permitted. • Addition of Section 10 The PrinciPIL 'Study within a Trials' Sub-study The PrinciPIL study has received an overarching REC/HRA approval to embed a SWAT study within 5 UK based clinical trials (REC reference 22/PR/0063, IRAS 305945). • Section 12.9 Cost effectiveness analysis updated • Appendix G updated. • Typographical errors corrected throughout document Amendment to the following documents: • New document: Patient Information Sheet SWAT V1.0 10 June 2022 • Updated Patient Information Sheet • Updated Non-responder letter post randomisation
11	10.0	04/10/2022	Dr Jonathan Sandoe Kelsey Armitage	• Updated screening process.

12	12.0	10/07/2023	Dr Jonathan Sandoe Kelsey Armitage	• The primary outcome has been changed from 'to determine whether the PAAP intervention is clinically effective in improving patient health outcomes' to 'Effects of PAAP on penicillin prescribing' • Additional secondary outcomes added 'Effect of PAAP on de-labelling' • Exploratory outcome added 'safety outcomes' • Removed the requirement for Pen-a testing to be completed at immunology clinics only. • Inclusion criteria updated to clarify that 'systemic antibiotics' are required in the last 24 months. Additionally note removed to allow participation of patients with a penicillin allergy label and a recently penicillin prescription. • Section 7.3 updated to ensure clarity that GP practices can continue to invite eligible patients. • Section 7.4 added the option for patients to use a 'Trial Partner'. • Section 7.9 updated to clarify that the notes review will be completed up to 12 months post randomisation and the SystmOne report will be used for data collection. • Removal of section relating to The PrinciPIL 'Study within a Trials' Sub-study as ALABAMA is no longer taking part

				• Section 11.2 sample size updated in response to updated primary outcome • Added information on the use of Sentry Amendments to the following document: • Patient Information Sheet • Post Allergy Testing Information Sheet • Post PAAP day 4-6 questionnaire • Post PAAP day 28-30 questionnaire • Post antibiotic day 2-4 questionnaire • Post antibiotic day 28-30 questionnaire • Verbal Consent Form • Face to face consent form Creation of new documents below: • GP non-allergic reaction letter • Letter with consent form • Trial partner letter
13	13.0	12/10/2023	Dr Jonathan Sandoe Kelsey Armitage	• exploratory outcome added 'Effects of PAAP on all outcomes for follow up past 12 month' • Clarification provided on the source of data for the primary outcome and secondary outcomes. • The cost effective analysis section has been updated in relation to SA12 and the change to primary outcome

				and further clarification has been provided on planned analysis for differences in costs and QALYs that are likely to accrue after the end of the 12 month trial follow-up Creation of new document below: • Privacy Notice to be published on the ALABAMA website detailing information collected from participants, how it is stored, and the purpose of collecting this, and who is responsible for this.
14	14.0	16 Nov 2023	Dr Jonathan Sandoe Kelsey Armitage	• Protocol updated throughout to allow all healthcare professionals involved in the trial to be interviewed as part of the process evaluation. Amendment to the documents below: • Clinician Interview Consent form • Clinician Interviews Information Leaflet • Privacy Notice

22. APPENDIX G: Common Infections managed in the community for which a penicillin is the first line recommended therapy

ALABAMA Infections for which an antibiotic prescription would be considered a primary event, and subsequently assessed for primary trial outcome.
Acute sore throat, pharyngitis, tonsillitis
Oral infection
Parotitis, salivary gland infection
Community acquired pneumonia
Chest infections i.e. 'acute bronchitis' or 'lower respiratory infection' or unspecified
Acute otitis media
Acute bacterial rhinosinusitis
Infective COPD exacerbation: amoxicillin or doxycycline first line unless patient at higher risk of treatment failure then co-amoxiclav; empirical treatment or guided by most recent sputum culture and susceptibilities
acute exacerbation of bronchiectasis
Skin and soft tissue infection (cellulitis, surgical wound infection, infected ulcer/pressure sore, erysipelas, boil, faruncule, impetigo etc)
Diverticulitis
Dental abscesses

ALABAMA Study pre-penicillin allergy test allergy history form

To be completed by research nurse during consultation with the trial participant

Date completed:_____/_____/ _____

Participant ID: _____

Part A. Patient Details

1. Month and year of birth:_____/_____/ _____

Part B. Check exclusion criteria

2. What allergic symptoms occurred after taking a penicillin? (Tick all that apply)

2.1 ☐ Rash (severe, i.e. needing hospital admission)
2.2 ☐ Rash (with blistering)
2.3 ☐ Swelling of the lips, tongue, throat
2.4 ☐ Swelling of other parts of the body
2.5 ☐ Difficulty breathing (including wheezing)
2.6 ☐ Collapse
2.7 ☐ Palpitations
2.8 ☐ Anaphylaxis

3. Did the reaction to antibiotics result in admission to hospital? (tick one)
☐ Yes ☐ No ☐ don't know

4. Did the reaction require treatment with? (tick all that apply)
☐ Adrenaline ☐ Steroids ☐ Antihistamine

5. Does the patient have unstable airways or unstable coronary artery disease?
☐ Yes ☐ No

6. Is the pregnant or breast feeding?
☐ Yes ☐ No

7. Is the patient taking any antihistamines or antihistamine containing drugs?
☐ Yes ☐ No

8. Are you currently taking or have you taken steroids within the last 10 days?
☐ Yes ☐ No

9. Has the patient taken betablockers in the previous 24 hours?
☐ Yes ☐ No

Action (tick one):

☐ Participant requires discussion with medical cover (ANY box in question 2 is ticked or ANY answer to question 3-9 is "Yes") complete part C but discuss with senior medical cover.

☐ Participant confirmed as suitable to proceed (NO box in question 2 is ticked AND all answers to question 3-9 are "No"), complete part C.

Part C. Selecting patients for direct oral challenge test or skin test plus oral challenge test

1. The name of penicillin that caused the allergic reaction? (tick all that apply)

   1.1 Penicillin V
   1.2 Penicillin G
   1.3 Ampicillin
   1.4 Amoxicillin
   1.5 Co-amoxiclav (other names: amoxicillin/clavulanic acid/Augmentin)
   1.6 Flucloxacillin
   1.7 Co-fluampicil (Flucloxacillin and ampicillin)
   1.8 Piperacillin/tazobactam (also known as Tazocin)
   1.9 Temocillin
   1.10 Pivmecillinam
   (also called amdinocillin pivoxil/Selexid/Penomax/Coactabs)

   1.11 Ticarcillin
   1.12 Don't know
   1.13 Other

   1.14. Please specify if other: _____

2. Was the reaction to penicillin more than 10 years ago? (tick one)

   ☐ Yes ☐ No ☐ don't know

3. What symptoms occurred? (Tick all that apply)

   ☐ 3.1 Urticaria or isolated facial swelling
   ☐ 3.2 Rash (no blistering, non-itchy)
   ☐ 3.3 Rash (no details known, e.g. rash as child)
   ☐ 3.4 Don't know/can't remember
   ☐ 3.5 Dizziness
   ☐ 3.6 Nausea
   ☐ 3.7 Vomiting
   ☐ 3.8 Abdominal discomfort or diarrhoea
   ☐ 3.9 Thrush
   ☐ 3.10 Other
   Please specify if "other": _____

4. When did the reaction occur, did you get the allergic reaction? (select only 1)
   ☐ After the first antibiotic dose and before the second dose
   ☐ After the second dose (during the course)
   ☐ Don't know

5 Since the penicillin allergy was diagnosed, have they taken any of the following antibiotics **without having an adverse reaction**? (please tick all that apply)

- ☐ 5.1 Penicillin V
- ☐ 5.2 Penicillin G
- ☐ 5.3 Ampicillin
- ☐ 5.4 Amoxicillin
- ☐ 5.5 Co-amoxiclav (also known as amoxicillin/clavulanic acid/Augmentin)
- ☐ 5.6 Flucloxacillin
- ☐ 5.7 Co-fluampicil (Flucloxacillin and ampicillin)
- ☐ 5.8 Piperacillin/tazobactam (also known as Tazocin)
- ☐ 5.9 Temocillin
- ☐ 5.10 Pivmecillinam
  (also known as amdinocillin pivoxil/Selexid/Penomax/Coactabs)
- ☐ 5.11 Ticarcillin

Action (tick one):
☐ Participant is suitable for direct oral challenge test using **low risk dosing schedule**:
Participant confirmed as suitable in Part B **AND**:
Any box in Q3.5– 3.9 is ticked, regardless of answer to Q2 or Q4
OR Boxes Q3.2 – 3.4 are ticked **AND** the answer to Q2 is 'Yes' or 'Don't know', AND answer to Q4 is "After second dose or don't know"

☐ Participant is suitable for skin testing before any oral challenge test **(use standard risk dosing schedule)**:
Participant confirmed as suitable in Part B **AND**:
Box 3.1 is ticked **OR**
Boxes 3.2-3.4 are ticked **AND** the answer to Q2 is 'No', **AND** answer to Q4 is 'After the first antibiotic dose and before the second dose'.

Completed by :……. Job Title:……

Date:……..... Signature:……..……..

Notes:

Part B
Q 2.7 Palpitations – a sensation of the heart beating fast that lasted more than a minute or required medical assessment
Q 2.8 The patient was told by a healthcare professional the reaction to antibiotics was "anaphylaxis"
Q 5 Unstable airways disease includes: Severe/brittle asthma or asthma requiring a course of steroids in the past 3 months
Q 5 Unstable coronary artery disease is that requiring daily use of sublingual or spray Glyceryle trinitate (GTN spray).
Q7a Antihistamines include: acrivastine, bilastine, cetirizine hydrochloride, desloratadine , fexofenadine hydrochloride, levocetirizine hydrochloride, loratadine, mizolastine, rupatadine,

alimemazine tartrate, chlorpheniramine maleate, clemastine, cyproheptadine hydrochloride, hydroxyzine hydrochloride, ketotifenpromethzine hydrochloride.
Q7b - Patient's who are taking antihistaminergic medication, for example amitriptyline, might still be suitable to continue with testing, if they do not need SPT and can proceed directly to OCT
Q9 Beta blockers include: Acebutolol, Atenolol, Betaxolol, Bisoprolol Fumarate, Carvedilol, Celiprolol Hydrochloride, Esmolol Hydrochlorid, Labetalol Hydrochlorid, Levobunolol Hydrochloride, Metoprolol Tartrate, Nadolol, Nebivolol, Phenoxybenzamine Hydrochloride, Pindolol, Propranolol Hydrochloride, Sotalol Hydrochloride, Timolol Maleate

Part C
Q3.1 Urticarial rash "Raised, red, itchy rash with each lesion typically lasting less than 24hrs (hives/urticarial)

A4.1 Example patient penicillin allergy assessment results card

Patient name: _____

Patient NHS number: _____

This patient underwent allergy testing to

_____

at Leeds Teaching Hospitals NHS Trust under the supervision of [redacted], Consultant in Clinical Immunology and Allergy on _____ [insert date]

A4.2 General practitioner penicillin allergy assessment information sheet

The test result was negative which means that this patient is not allergic to

_____

and can be prescribed penicillin antibiotics with the same risk as the general population.

ALABAMA
ALlergy AntiBiotics And Microbial resistAnce

NHS
The Leeds Teaching Hospitals
NHS Trust

Penicillin Allergy Testing

Information for general practice

This document is designed to give you information about penicillin allergy testing and what a negative test result means. It is provided as part of the ALABAMA research study.

Part 1: Penicillin allergy record and its implications

A true penicillin allergy is an adverse drug reaction with an established immunological mechanism; it can involve symptoms such as rash, but also difficulty breathing, swollen lips, tongue or face often at the same time.[1] Reactions can be fatal, but this is very rare: 0.9–20 deaths per million patients treated with penicillin.[2] There is no evidence that penicillin allergy is hereditary.

Incorrect penicillin allergy records are very common

About 10%–20% of the UK population report penicillin allergy, but less than 1 in 10 people who think they are allergic have a confirmed allergy to penicillin.[1, 3, 4]
Reasons for incorrect diagnosis of penicillin allergy include symptoms of illness or side effects being mistaken for allergy, incomplete or inconsistent documentation of allergy in medical records; or patients receiving the allergy diagnosis in childhood.

Incorrect penicillin allergy records can be harmful for patients

There are important consequences of patients being incorrectly identified as allergic to penicillin:

- **Adverse patient outcomes:** Patients with a penicillin allergy record often do not receive optimal standard-of-care treatment/or prophylaxis; are increased risk of mortality; have longer hospital stays, and; are more likely to be admitted to the ICU. [3]
- **Effect on antimicrobial prescribing**: Patients with a penicillin allergy record are more likely to be prescribed broad-spectrum antibiotics such as quinolones, macrolides, clindamycin, tetracycline, sulphonamides, and third-generation cephalosporins.[1, 5] These alternative, broader spectrum and often more expensive treatments can have reduced efficacy, resulting in additional treatment failures. [6] Patients are also more likely to receive more than one antimicrobial prescription during hospitalisation when compared with patients without a penicillin allergy record.[3]
- **Antimicrobial resistance**: By being prescribed broad spectrum antibiotics more often, patients are at increased risk of acquiring multi-drug resistant bacteria, including Clostridium difficile and MRSA.[5, 7, 8]

Part 2: Penicillin allergy testing

What does the test involve?

Penicillin allergy testing will take place at a specialist allergy clinic at St James' Hospital, Leeds. The test involves 2 or 3 stages. It will take place during a single clinic visit (half a day).

Stage 1: Patient history

A doctor or nurse will take the patient history including details on the timing and the severity of the allergic reaction, symptoms experienced, characteristics of reaction and the route of penicillin administration. If there is uncertainty about whether the patient is truly allergic to penicillin, they will be referred to stage 2 or 3 as appropriate.

Stage 2: Skin test

A small amount of penicillin in a liquid form will be injected into the patient's forearm. Patient skin will be examined after 15 minutes. If the patient is allergic to penicillin, then they are likely to experience a red weal in the area of the scratch. Some people may need a second skin test; if that is the case this will take around 45 minutes. Patients will be closely monitored. Most patients do not have a reaction and go on to stage 3. Patients with a positive skin test will not proceed to stage 3.

There is evidence that patients can safely miss out the skin test in Stage 2 if their index reaction to penicillin (on which the allergy label was based) was mild or involved symptoms which were likely to be side effects.

Stage 3: Oral challenge

Oral challenge is the gold standard test for penicillin allergy. It is still required in patients with a negative skin test because false negative skin tests do occur [9].Patients will be tested to the penicillin that caused their reaction, or in cases where this is unknown, amoxicillin will be used, as it is the most frequently prescribed penicillin. Patients will be given three doses over an hour period; 50mg/1ml, 250mg/5mls, 200mg/4mls. Patients will be continuously monitored in the allergy clinic during the test and for an hour after.

If patients have no reaction during this time they will be given a 3-day course of penicillin to take at home and will be followed up by telephone by an allergy nurse to check for delayed reactions.

How accurate is the test?

The test offered to patients is highly accurate; the combination of negative skin testing and negative oral challenge testing has been found to have >99% negative predictive value for true pen-allergy.[10] Oral challenge tests are the gold standard for excluding penicillin allergy because skin prick tests alone do not have a high negative predictive value; a third of allergic patients who pass skin prick tests are only diagnosed as allergic after an oral challenge.[11]

A negative test does not guarantee that patients will not have an allergic reaction in future. However, the risk is the same as that for the general population (the incidence of true penicillin allergy is estimated to be 0.005% for oral administrations and 0.002% for IV administration [12]).

Are there any risks to patients having the test?

Penicillin allergy testing is low risk. Patients invited for a test will be screened and excluded if they are at signifi risk of allergy to penicillin. This ensures that only patients who are really unlikely to be allergic are offered the oral challenge test.

Skin prick testing is generally safe and systemic reactions following testing are rare. [13] Studies have used penicillin oral challenge in patients with positive histories of penicillin allergy but negative skin test results: the vast majority of patients tolerated the challenge and those who did not experienced only urticarial or mild skin reactions. [4] As an additional safety measure, patients with a positive skin test will not undergo the oral challenge.

The staged approach to assessment has been developed for this trial to minimise the risk of harm to patients whilst also providing optimal diagnostic accuracy. Each stage of the testing has been risk assessed based on published data, clinical experience locally and nationally, and expert opinion to minimise risk of harm.

During each stage of the test patients will be closely monitored by a doctor or nurse who will be trained to deal with any severe allergic reactions. It is possible, but very unlikely, that patients may need to stay in hospital overnight following this test, if they experience a severe reaction.

When patients take a course of penicillin at home, following their clinic visit, it is possible they may develop symptoms such as malaise, a mild, localised rash, nausea, GI upset, or other mild symptoms. These are likely to be side effects from amoxicillin rather than true allergy. It is extremely unlikely that they will have any serious symptoms, as these would have happened when they took penicillin during the clinic visit. Patients will be able to call the hospital allergy clinic if they are concerned and they will be advised what to do. You will also be provided with a number to call in case you have any questions or concerns.

How should I discuss the test with patients?

Patients may be more likely to attend testing if it is encouraged by their GP. Patients in the ALABAMA Study randomised to the intervention arm will receive a booklet giving details about the importance of testing and the potential benefi [see leafl "***Penicillin allergy testing: going for a test***"]. You can discuss this booklet with patients to answer any queries and help patients to understand the benefi of the test and why removing their penicillin allergy record, if found incorrect, might be good for them (as above).

Part 3: The test result: next steps

Updating patient records

You will receive confi that your patient has completed the penicillin allergy test and that their result is either positive (allergic) or negative (not allergic). Incorrect allergy labels should be removed with a record of why this change has been made.

Discussing the test result with patients

Patients in the ALABAMA study will receive a letter informing them of their test result. Patients who have a negative test result will be provided with a leafl explaining this result [see leafl "***Penicillin allergy testing: A negative test result***"]. Patients will also be given a card to carry on them to confi which test they have had and the negative result. Patients may show you this card when they attend for care in future.

The result of the test should be discussed with patients when they next consult and/or when they are next prescribed an antibiotic. Patients should be reassured that their test was negative which means they can safely take penicillin-based antibiotics. You should confi with patients that the allergy label has been removed from their records.

Prescribing penicillin after a negative test

After a negative test, patient can now take penicillin antibiotics including: amoxicillin, ampicillin, benzylpenicillin, co-amoxiclav, co-fl fl xacillin, penicillin V, piperacillin with tazobactam, pivmecillinam and temocillin. Patients are warned that there is a still a possibility they might react to an antibiotic they are prescribed in the future. In the population of low risk patients being assessed in the ALABAMA trial, the risk of a patient having an allergic reaction to penicillin in those patients who were once labelled as penicillin allergic, but who tested negative according to these procedures, is the same as that for the general population.

You may wish to remind your patient that they have been tested for penicillin allergy and they are no longer allergic. You can also refer them to the patient booklet on a negative test result (see above).

Patients may still experience side effects after taking penicillin. These may include: localised rash, feeling sick, vomiting, diarrhoea, stomach pain or feeling bloated. You may want to warn patients that they may experience these side effects but that these symptoms do not necessarily mean that they are allergic to penicillin. If a patient develops side effects to one type of penicillin, they can still be prescribed other types of penicillins.

References:

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This document was designed by clinicians and researchers at the University of Oxford, University of Leeds and Leeds Teaching Hospital NHS Trust as part of the ALABAMA study.

Penicillin Allergy Testing

Going for a test

ALABAMA
ALlergy AntiBiotics And Microbial resistAnce

NHS
The Leeds Teaching Hospitals
NHS Trust

UNIVERSITY OF OXFORD
NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

UNIVERSITY OF LEEDS

HOW CAN THIS BOOKLET HELP ME?

This booklet is designed to give you information about penicillin allergy testing if you have been referred by your doctor. It will explain how you may benefit from penicillin allergy testing and what the test involves.

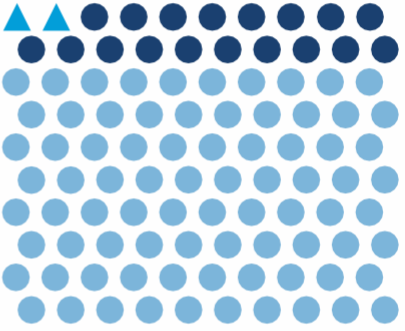
Cover image: iStock.com/ SolStock; inside cover: Pexels.com

HOW DO I KNOW IF I AM ALLERGIC TO PENICILLIN?

About 10-20% of people think, or have been told, that they are allergic to penicillin. In fact, **fewer than 1 in 10 people who think they are allergic, actually do have an allergy to penicillin.**

Up to 20% of people think, or have been told, that they are allergic to penicillin.

Only 1 in 10 people who think they are allergic, actually do have an allergy to penicillin



There are different reasons why people may have an incorrect label of penicillin allergy. It can be difficult for patients and their GP to identify when someone has an allergic reaction to penicillin. Often, common side effects of penicillin are mistaken for allergy. This includes problems such as sickness, diarrhoea, stomach ache, and thrush. Sometimes, the illness which you were taking penicillin for, causes symptoms which are mistaken for allergy. Lots of people have just always been told to avoid penicillin, because of a problem in childhood which they can't remember.

Once the penicillin allergy label is on your medical records, it is rarely questioned, and can be very difficult to remove.

A penicillin allergy test is the safest way to find out whether or not you are allergic to penicillin.

WHY IS IT IMPORTANT FOR PEOPLE TO HAVE A PENICILLIN ALLERGY TEST?

There are several different types of antibiotics called 'penicillins'; they are all in a group called 'beta-lactam' antibiotics. Penicillin antibiotics include penicillin V, ampicillin, flucloxacillin, amoxicillin and many others. These antibiotics are very useful for treating lots of different infections, including ear, skin, throat and chest infections and **are very safe to take. They are often the preferred, best treatment for infections.**

It is important for your medical record to be accurate to make sure you get the best care when you are ill. Having an incorrect pencillin allergy record means that your doctor cannot prescribe penicillin antibiotics for you.

When people have a label of penicillin allergy, they have to be given different antibiotics, not penicillins. These **other antibiotics may be less effective** at treating their infection, and can increase the risk of 'superbug' infections such as Clostridium difficile (C.diff) and Methicillin-resistant Staphylococcus aureus (MRSA).

If a test shows that you are not allergic to a penicillin, you can safely take that penicillin antibiotic. In the NHS, if you are tested and do not react to a penicillin, then it is assumed you can safely take all penicillins. There is still a tiny risk that you might react to another penicillin in the future, but this is true for all drugs and needs to be balanced with the risks of not taking penicillins. Being able to take penicillin will make it easier for your doctor to prescribe you an antibiotic if you need it as they will be able to prescribe the "first choice", best treatment. It would mean that you would not have to take different antibiotics which may not work as well as penicillin.

Penicillin is a narrow spectrum antibiotic, which means it is an antibiotic which only targets the specific bacteria which cause the infection and does not kill "good" bacteria. Taking penicillin antibiotics instead of other antibiotics means that you would be helping to fight antibiotic resistance which is an important public health problem.

WHAT DOES A PENICILLIN ALLERGY TEST INVOLVE?

Penicillin allergy testing takes place in a hospital, in a specialist allergy clinic. It has either two or three stages.

1. Taking your history

A doctor or nurse will ask you about your penicillin allergy, the problems you had when you took a penicillin antibiotic, and when the problem happened. Many people won't know the answers to these questions, which is fine.

2. Skin testing

A skin test is where a doctor or nurse injects a tiny amount of penicillin-containing liquid into your forearm. This is slightly painful, like a mosquito bite. The doctor or nurse will monitor you to see how your skin reacts to penicillin. If you are allergic to penicillin then your skin may have itchy, red raised bumps in the area of the test. Your skin will be examined after 15 minutes. Some people may need a second skin test; if that is the case this will take around 45 minutes. Most people do not have a reaction and go on to stage 3.

You can safely miss out the skin test if your previous reaction to penicillin was mild or involved symptoms which were likely to be side effects, or happened a long time ago.

3. Trying penicillin

A doctor or nurse will either give you:
- A small amount (half a teaspoonful) of a penicillin syrup, followed by 2 teaspoonfuls, and then 4 teaspoonfuls, if you feel ok. This procedure takes around two hours and you will be monitored by a doctor or nurse for the whole time. After the last dose, you will stay in the clinic for another hour.
- Or one full dose (dependent on your allergy history)

If you have no reaction, you will be asked to take a penicillin at home for 3 days. This is long enough to check for any delayed reaction. When taking the penicillin at home you may experience symptoms which could be due to a delayed reaction or to side effects. These symptoms are generally mild and do not require treatment.
You will be provided with details of who to call if you have any symptoms or concerns.

A doctor or a nurse at the clinic will call you after you have finished taking the penicillin at home. They will ask you whether you have had any symptoms which may indicate that you had a delayed allergic reaction. You will be sent a letter giving you the result of your test after this phone call. If you had no problems taking penicillin you will have your allergy status changed on your hospital records to 'not allergic'. Your GP will receive a letter about your test result and will update your GP medical records. You will be tested to the penicillin that caused your reaction, or if you don't know what that was, amoxicillin will be used, because this is the most commonly prescribed penicillin.

ARE THERE ANY RISKS TO HAVING A TEST?

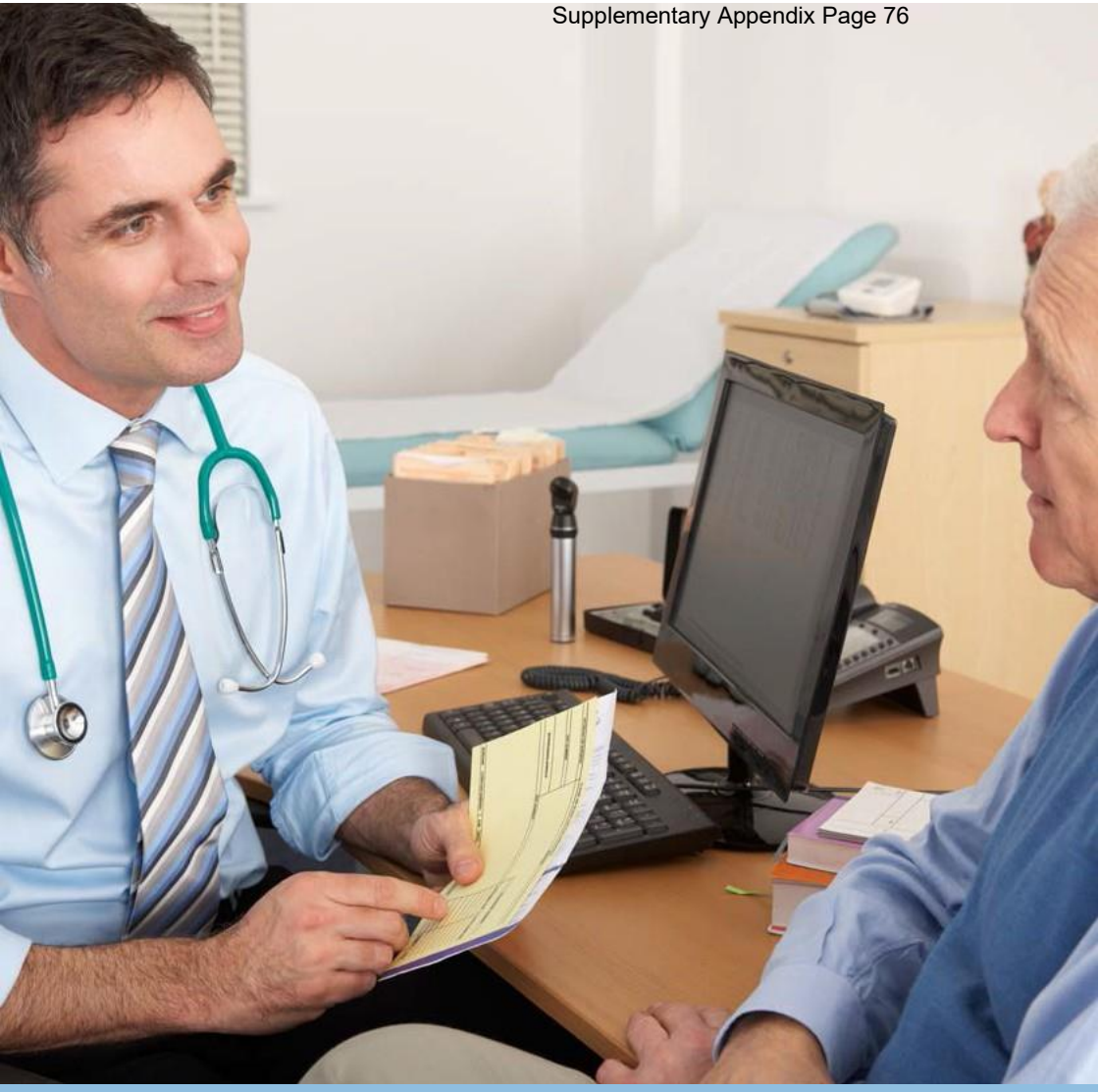
Penicillin allergy testing is very safe. During each stage of the test you will be closely monitored by a doctor or nurse.

You will only be offered this test if a doctor or nurse in the allergy clinic think that you are not allergic to penicillin. However it's not possible to guarantee that you won't have an allergic reaction to penicillin during the test, because there is a risk of this when you take any drug or medicine.

If you have a reaction during the clinic visit, you might feel sick, itchy, develop hives ('nettle rash'), swelling, a fast heartbeat, dizziness or difficulty breathing. If someone has an extremely serious reaction, this could be fatal, but this is very rare. If you have any reaction, you will be treated immediately by fully trained medical staff until you get better. It is possible, but very unlikely, that you may need to stay in hospital overnight following this test as a result of having a serious reaction.

Once you go home, it is possible you may develop mild symptoms such as sickness, a mild, small rash, nausea, upset stomach, or other mild symptoms. It is extremely unlikely that you will have any serious symptoms, as these would have happened when you took penicillin during the clinic visit. You will be provided with details of who to call if you have any symptoms or concerns.

This document was designed by clinicians and researchers at the University of Oxford, University of Leeds and Leeds Teaching Hospital NHS Trust as part of the ALABAMA study.



Penicillin Allergy Testing

A negative test result

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NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

UNIVERSITY OF LEEDS

WHAT DOES A NEGATIVE TEST RESULT MEAN?

A negative test result means that you are not allergic to penicillin. During the test you took a type of penicillin antibiotic, and medical staff monitored you to see how your body responded. As you experienced no major problems during the test and no symptoms of allergy your doctor has confirmed that you are no longer allergic to penicillin.

A negative test means that you are now able to take all antibiotics in the penicillin group (beta-lactam antibiotics), which previously were not available to you. These include: amoxicillin, ampicillin, co-amoxiclav, co-fluampicil, flucloxacillin, and penicillin V.

These antibiotics are very good at treating common bacterial infections such as skin, ear, sinus or throat infections. They are also very safe. They are often the preferred, best treatment for infections.

IS IT SAFE FOR ME TO TAKE PENICILLIN NOW?

Yes, the test you had is very accurate in identifying whether patients have a true penicillin allergy. The test was designed based on the latest allergy guidelines in the NHS. You can now safely take all antibiotics in the penicillin group (beta-lactam antibiotics).

The negative test does not guarantee that you will never have an allergic reaction in the future. However, the risk of that is very low and similar to people who never had an allergic reaction. In the very unlikely event that you have any symptoms when taking penicillin next time, you should talk to your GP who will be able to advise you on the next steps.

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WHAT SHOULD I DO NOW?

Keep your results letter safe so you can refer to it, when needed. Your GP has also received a letter describing the test you had and stating that you had a negative result. They will update your medical records at your practice and remove the penicillin allergy label. You can ask your GP the next time you see them whether your records have been updated.

You can also let your family know that you are no longer allergic so that if you ever need hospital care they can advise on your behalf that you are not allergic to penicillin.

WHAT SHOULD I DO NEXT TIME I HAVE AN INFECTION?

Your GP will be able to advise you whether you need antibiotics. If you do need antibiotics, you can remind your GP that you have been tested for penicillin allergy and you are no longer allergic. It is possible that penicillin might not be the best antibiotic for your particular infection, in which case your GP might prescribe a different antibiotic.

We have provided a card for you to keep which can be carried with you to allow you to show any health professional the results of your test. The card gives details about the allergy test you completed and explains you had a negative result which means you are not allergic to penicillin.

This document was designed by clinicians and researchers at the University of Oxford, University of Leeds and Leeds Teaching Hospital NHS Trust as part of the ALABAMA study.

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Standard Operating Procedure	Oral Challenge Test - Penicillins
Version No.	V5.0

Contributor	**Name**	**Date**	**Signed**
Written by:	[redacted] Research Nurse	01.10.20	[redacted]
Updated by:	[redacted] Research Fellow	06.05.22	
Approved by:	[redacted] Consultant Immunologist	06.05.22	

Filename:	ALABAMA SOP - Oral Challenge Test - Penicillins.docx
Location of copies:	1. Clinical Immunology & Allergy, Ground Floor, Beckett Wing, SJUH 2. ALABAMA Investigator Site File, Infection Research Office, Level 8 Gledhow Wing, SJUH. 3. ALABAMA Study Folder, Infection Research Network Drive 4. ALABAMA 'PAAP SOPs' folder, shared 'N' drive, UoL

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Standard Operating Procedure

Oral Challenge Test to Penicillins

The following standard operating procedure outlines how to perform an Oral Challenge Test to penicillins and is applicable to all health care professionals undertaking this role.

In the diagnosis of drug allergy an oral challenge test is considered the 'gold standard' due to the unreliability of other testing methods. An oral challenge test (OCT) involves administering the test drug in increasing doses until a reaction occurs or the usual prescribed dose level is reached. Alternatively patients can be given a single dose, where the risk of possible reaction is judged to be extremely low.

Oral Challenge Testing to penicillins should only be performed by an appropriately trained and competent healthcare worker who is also trained in recognition and treatment of anaphylaxis.

EXCLUSIONS

- Antihistamines within 72 hours of OCT
- Beta-blocker within 24 hours of OCT
- Steroids within 10 days of OCT
- History of Anaphylaxis
- History of Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, acute interstitial nephritis, hemolytic anemia, and drug rash with eosinophilia and systemic symptoms (DRESS)
- Severe/brittle asthma or unstable coronary artery disease
- Pregnancy
- Currently taking antibiotics for active infection*

*Long term prophylactic antibiotics may be continued in certain scenarios after discussion with the medical team.

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EQUIPMENT:

- 100mL Amoxicillin 250mg/5mL (or different when index Penicillin is known)
- 50mL Sodium Chloride 0.9%
- Oral Challenge Test Prescription Chart **(Appendix 4)**
- Observational monitoring chart **(Appendix 3)**
- PPE - Follow current LTHT guidelines (available on LTHT Intranet)
- Syringes 1mL, 2.5mL & 10mL
- Sharps bin
- Timer (clock/watch)
- Emergency equipment available to treat anaphylaxis
- 18G Needles
- Needle free device (Bionector connector)
- IV cannulation pack: Steret, gauze, 20G cannula, tegaderm (n.b cannulation prior OCT is not needed routinely for patients deemed to have low risk of reaction)

PREPARATION:

The procedure should be undertaken in accordance with LTHT Covid-19 Coronavirus Guidelines and local infection control policy.

Perform positive ID check, ensure prescription is valid and rescue medications are prescribed (Refer to prescription chart). Discuss the procedure with the patient; written consent for the procedure must be obtained. The procedure must only be undertaken if the patient is well. Check current health status/ current medications with patient and SystmOne. The test must be cancelled if the patient has intercurrent infection, uncontrolled asthma, cardiac problems, or has taken medications likely to interfere with the challenge test (see Exclusions & Cautions).

PROCEDURE:

1. Perform hand hygiene and don any outstanding PPE.

2. Perform a set of baseline observations (BP, Pulse, Sp02) and document.

3. Ensure patient is in a comfortable position.

4. Some patients will require cannulation as confirmed by the medic on duty.

5. The following **standard** dosing regimen should be used routinely. For patients who are deemed **low risk** use the dosing schedule outlined in Appendix 5.

6. Administer 10% of the standard dose of the test drug (e.g. usual dose of amoxicillin or penicillin V = 500mg - start with 50mg) and document.

7. Ask the patient to report any adverse reaction **(Appendix 1)**, monitor for 15-20 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

8. If no reaction or significant change in observations then administer further 25% of the standard dose of the test drug (e.g. 125mg of amoxicillin or penicillin V when the standard dose is 500mg) and document.

9. Ask the patient to report any adverse reaction **(Appendix 1)**, monitor for 15-20 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

10. If no reaction or significant change in observations then administer the final standard dose (500mg of amoxicillin or penicillin V) and document.

11. Ask the patient to report any adverse reaction **(Appendix 1)**, monitor for 30 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

12. Document test result and reactions in **Appendix 3** and explain the results of the test to the patient.

13. Supply the patient with the remaining 100ml of the appropriate antibiotic (amoxicillin/penicillin V or other) used in the challenge test, as prescribed for home dosing.

14. Beginning with the first dose on the evening of the oral challenge test, instruct the patient to take the standard dose of the appropriate antibiotic (500mg of amoxicillin or penicillin V) three times daily until the course is completed.

15. Refer to AFTERCARE and provide the patient with the post allergy testing information sheet.

16. Once the D4-6 follow-up call is completed, scan and email appendix 3 (with all other PAAP testing documentation) to the Allergy/Immunology secretaries for upload to patient electronic health records (e.g.PPM+).

INTERPRETATION:

Any positive reaction **(Appendix 1)** should be documented and the test stopped.
Reactions should be treated appropriately - See **Appendix 2.**

COMPLICATIONS:

Although OCT is a common procedure and regarded as safe, the possibility of a systemic reaction remains a possibility.

AFTERCARE:

If no adverse reaction has occurred, the patient is free to leave the clinic.
In case of late phase response, the patient must be instructed to call 111 or visit their local Emergency Department should they develop symptoms of dyspnoea, wheezing, dizziness or severe pruritus.

Appendix 1: Signs & Symptoms of allergic reactions in various target organs.

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Skin:	Urticaria/Angioedema
	Flushing
	Erythematous pruritic rash
	Atopic dermatitis
Gastro-intestinal tract:	Pruritis and /or swelling of the lips, tongue or oral mucosa
	Nausea*
	Abdominal cramping or colic*
	Vomiting or reflux*
	Diarrhoea*
Respiratory tract:	Nasal congestion
	Rhinorrhoea
	Pruritis/sneezing
	Laryngeal oedema, staccato cough and/or dysphonia
	Wheezing/ repetitive cough
Cardiovascular:	Hypotension/shock
	Dizziness

* Any of these occurring in isolation are unlikely to be indicative of an allergic reaction

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Appendix 2: Treatment of positive reactions during oral challenge testing.

Mild reactions:

- Ensure patient is comfortable
- Administer 10mg Cetirizine orally and monitor patient.

Severe reactions:

- Contact medical team
- Assist patient into a comfortable position; recovery position for hypotension/faintness, upright for dyspnoea
- Administer oxygen and nebulised salbutamol if required
- Prepare anaphylactic pack to administer 0.5mL adrenaline 1:1000 Intra-muscular
- Call Resuscitation Team if necessary
- Commence CPR if required.

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Appendix 3: Observational monitoring chart

Date:	**Drug & Concentration Tested:**	**Patient Name:**
		NHS No:

Time	Dose Administered	Blood Pressure	Pulse	Sp02	Symptoms/Reactions

Testing performed by :…… Signature:…….. Date:……..…

Document the result of the test clearly in the box below (After the D4-6 follow-up call):

RESULT OF TEST:	**NEGATIVE**	**POSITIVE**
ADVICE FOR PATIENT	SAFE TO TAKE DRUG AGAIN IN FUTURE	MUST AVOID DRUG IN FUTURE

Test result completed by: …… Signature:…….. Date:……..…

Appendix 4: Oral Challenge Test Prescription Chart

First Name:		Surname: (Block Letters)
Hospital No:	NHS No:	DOB:
Consultant: (Use addressograph if available)	Ward:	Hospital:

Allergies and Adverse Drug Reactions - List the medicines or substances & the nature of the reaction (write NKDA if none)	
It is mandatory to complete this section	
Medicine/substance:	Sign (NAME):
Reaction:	Date:

Drug	Dose	Route	Prescribers Signature	PRINT name & Contact no.	Date	ADMINISTRATION		
						Date	Time	Sign

FOR EMERGENCY USE IN CASE OF ALLERGIC REACTION

Drug	Dose	Route	Prescribers Signature	PRINT name & Contact no.	Date	ADMINISTRATION		
						Date	Time	Sign
Cetirizine	10mg	PO						
Chlorphenamine	10mg	IV						
Hydrocortisone	100mg	IV						
Salbutamol	5mg	Nebs						
Adrenaline Auto-Injector	500mcg	IM						

Compiled by:…… [redacted] .Date:…19 Aug 2019……Approved by:… [redacted] .. Date:……02 Sep.2019…..

Oral Challenge Test Prescription Cha Version 1.0 02/09/2019

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Appendix 5: Alternative dosing schedule for **low risk patients** (e.g. those who are suitable for direct oral challenge test without prior skin testing)

1. Perform a set of baseline observations (BP, Pulse, Sp02) and document

2. Administer 100% of the standard dose of the test drug (e.g. usual dose of Amoxicillin or penicillin V = 500mg) and document.

3. Ask the patient to report any adverse reaction **(Appendix 1)**, monitor for 30 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

4. Monitor for a further 30 minutes, ask the patient to report any adverse reactions **(Appendix 1)** and perform a set of observations (BP, Pulse, Sp02) and document.

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Appendix 6: Alternative dosing schedule (to be used if indicated after discussion with a consultant immunologist)

1. Administer 1% of the standard dose of the test drug (e.g. usual dose of amoxicillin or penicillin V = 500mg - start with 5mg) and document.

2. Ask the patient to report any adverse reaction (Appendix 1), monitor for 15-20 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

3. If no reaction or significant change in observations then administer further 10% of the standard dose of the test drug (e.g. 50mg of amoxicillin or penicillin V when the standard dose is 500mg) and document.

4. Ask the patient to report any adverse reaction (Appendix 1), monitor for 15-20 minutes and perform a set of observations (BP, Pulse, Sp02) and document.

5. If no reaction or significant change in observations then administer further 50% of the standard dose of the test drug (e.g. 250mg of amoxicillin or penicillin V when the standard dose is 500mg) and document.

6. If no reaction or significant change in observations then administer the final standard dose (500mg of amoxicillin or penicillin V) and document.

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BIBLIOGRAPHY:

Wood, P. (2016) Protocol for: Open oral drug challenge testing. Leeds Teaching Hospital NHS Trust.

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Appendix 5.2: Skin Prick and Intradermal Allergy Test SOP

Standard Operating Procedure	Skin Prick and Intradermal Allergy Test
Version No.	V4.0

Contributor	**Name**	**Date**	**Signed**
Written by:	[redacted] Research Nurse	01.10.20	[redacted]
Updated by:	[redacted] Research Fellow	10.05.22	[redacted]
Approved by:	[redacted] Consultant Immunologist	10.05.22	[redacted]

Filename:	ALABAMA SOP – Skin Prick Intradermal Allergy Test.docx
Location of copies:	1. Clinical Immunology & Allergy, Ground Floor, Beckett Wing, SJUH 2. ALABAMA Investigator Site File, Infection Research Office, Level 8 Gledhow Wing, SJUH. 3. ALABAMA Study Folder, Infection Research Network Drive 4. ALABAMA 'PAAP SOPs' folder, shared 'N' drive, UoL

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Standard Operating Procedure

Skin Prick and Intradermal Testing

The following standard operating procedure outlines how to perform a skin prick test and is applicable to all health care professionals undertaking this role.

Skin prick (SPT) and intradermal (IDT) testing (SPT) are methods used to determine the presence of specific Immunoglobulin E (IgE) mediated reactions. SPT and IDT should be performed by an appropriately trained and competent healthcare worker who is also trained in recognition and treatment of anaphylaxis.

EXCLUSIONS:

SPT and IDT reactions are inhibited by antihistamines and may be inhibited by tricyclic antidepressants, tetracyclic antidepressants, topical corticosteroids and UV light treatment. Where possible inhibitory medication should be stopped at least 72 hours prior to testing,
Note - Patient's who are taking antihistaminergic medication, might still be suitable to continue with oral challenge testing if they do not need SPT.

CAUTIONS:

Caution should be taken when considering SPT/IDT in pregnancy, for patients with unstable asthma or those taking beta blockers and/or ACE inhibitors.

EQUIPMENT:

SPT and IDT

- PPE - Follow current LTHT guidelines (available on LTHT Intranet)
- Skin Marker/Pen
- Sharps bin
- Tissue Paper
- Micropore tape
- Skin test measure
- Timer (clock/watch)
- Emergency equipment available to treat anaphylaxis.
- ADULT Skin Prick & Intradermal Testing - Medications (**Appendix 1**)

SPT

- Positive control - Histamine 10mg/mL in 50% glycerol and 50% buffered 0.9% sodium chloride
- Negative control - 50% glycerol and 50% buffered 0.9% sodium chloride
- Test allergen solution (Amoxicillin 20mg/ml, +/- index penicillin if different to these). *
- Individual sterile skin prick testing lancets

IDT

- Negative control-normal saline (NB positive control is not used in IDT)
- Test allergen solution (Amoxicillin 20mg/ml, +/- index penicillin if different to these). *
- Needle 30G
- Syringe 1mL
- Alcohol wipe

* *Refer to **Appendix 2** for instructions for how to make testing dilutions.*

PREPARATION:

The procedure should be undertaken in accordance with LTHT Covid-19 Coronavirus Guidelines and local infection control policy.

Perform positive ID Check, discuss procedure with patient and gain verbal consent. Check current medications with patient & SystmOne (see Exclusions & Cautions). Select appropriate test site free from eczema / dermatitis, the preferred site is the forearm.

PROCEDURE:

STP and IDT

1. Ensure the patient is in a comfortable sitting position or, if needle phobic, lying down. Rest arm on a level surface, using a pillow if necessary.

2. Perform hand hygiene and don any outstanding PPE.

3. Remove appropriate garments to expose the testing site (typically skin of the forearm).

4. Assess the injection site for signs of inflammation, oedema, infection, and skin lesions.

SPT

5. Ensure test site is free from body lotion and moisturisers. The Test site should be hygienically clean but does not need to be cleaned with alcohol or antiseptic. Do not rub the area as this will create erythema.

6. Beginning with the positive control and ending with the test allergens (Amoxicillin, +/- index penicillin if different to these) use micropore tape to mark the test sites approximately 2.5cm apart, using first letter of allergen/control being tested (e.g. +, -, A). Place marked micropore tape on midline of forearm. Avoid the skin creases (elbow and wrist).

7. Place one drop of each selected allergen solution on the skin next to relevant marked site.

8. Using gentle pressure, push the lancet through allergen solution and into the surface layer of the skin.

9. Discard lancet into sharps bin.

10. Repeat the procedure for each allergen and the controls using a new lancet each time.

11. Remove surplus allergen by blotting test sites with tissue paper ensuring that no cross contamination between test sites occurs.

IDT (if SPT is negative and if indicated please proceed to IDT)

1. Attach 30G needle to 1ml syringe containing test solution / article.

2. Apply gloves and clean the injection site with a swab saturated with isopropyl alcohol 70% and apply gloves.

3. Remove the needle sheath and hold syringe with the dominant hand with the bevel of needle pointing up.
4. Beginning with the negative control use the non-dominant hand to stretch skin over the site with forefinger and thumb.

5. With the syringe almost against the patient's skin, insert the needle into the skin at an angle of 10–15° and advance through the epidermis so the needle tip can be seen through the skin.

6. Inject medication slowly. It is not necessary to aspirate as the dermis is relatively avascular.

7. While injecting medication, a bleb (resembling a mosquito bite) will form.

8. When a 3-5mm bleb is observed withdraw the needle rapidly. Do not massage the site.

9. Dispose of contaminated sharps into sharps bin.

10. Using skin marker draw around the formed bleb.

11. Repeat the procedure for each allergen and the controls.

SPT and IDT

1. Advise patients not to scratch the test sites whilst waiting for the results to develop.

2. Ask patients to report any systemic adverse reaction (e.g. dyspnoea, dizziness).

3. Results should be read 15-20 minutes after the test. Measure the wheal diameter in mm. For asymmetric wheals measure the longest extent of the wheal in mm and the extent 90° to the first measurement (e.g. 3x3mm).

4. Record the outcome of the test in the source document.

5. Topical 1% hydrocortisone, oral anti-histamines or a cold compress may be given to relieve severe itch in line with a prescription.

INTERPRETATION:

Test sites are examined for wheal or flare after 15 - 20 minutes has elapsed. For SPT any site with a wheal diameter of ≥ 3mm compared to negative control is considered a positive result. For

IDT any site with a hive and associated redness and swelling outside the marked area ≥ 3mm compared to the initial bleb or negative control is considered a positive result.

COMPLICATIONS:

Mild pruritus localised to positive test sites is the most common complication and usually resolves with no intervention.

Although SPT is a common procedure and regarded as safe, the possibility of a systemic reaction remains a possibility.

AFTERCARE:

If no adverse reaction has occurred, the patient is free to leave the clinic.

In case of late phase response, the patient must be instructed to call 111 or visit their local Emergency Department should they develop symptoms of dyspnoea, wheezing, dizziness or severe pruritus.

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Appendix 1: ADULT: Skin Prick & Intradermal Testing - Medications

Have any antihistamines, corticosteroids, anti-depressants, antipsychotics or ACE inhibitors been taken recently?

Yes / **No** (Please circle)

If **YES**: Drug:…… …. Last taken:……

Drug:…… …. Last taken:……

Clinic date:……

First Name:		Surname: (Block Letters)
Hospital No:	NHS No:	DOB:
Consultant: (Use addressograph if available)	Ward:	Hospital:

Drug/Allergen	Dilution	SPT Drug/Allergen Required	Wheal Size (mm) Time:	IDT Drug/Allergen Required	Wheal Size (mm) at time zero Time:	Wheal Size (mm) at 15mins Time:
Positive Control - Histamine	10mg/mL	Prescriber Initials		Prescriber Initials		
Negative Control - Sodium Chloride	0.9%	Prescriber Initials		Prescriber Initials		
AMOXICILLIN	20mg/mL	Prescriber Initials		Prescriber Initials		
BENZYLPENICILLIN	6mg/mL	Prescriber Initials		Prescriber Initials		
CO-AMOXICLAV	20mg/mL	Prescriber Initials		Prescriber Initials		
FLUCLOXACILLIN	20mg/mL	Prescriber Initials		Prescriber Initials		

Prescribed by:	Signature:	PRINT name and contact details:	Date:
SPT administered by:	Signature:	PRINT name and contact details:	Date:
IDT administered by:	Signature:	PRINT name and contact details:	Date:

Compiled by: [redacted] ..Date:…19 Aug 2019……Approved by:… .. [redacted] ….. Date:……02 Sep 2019…..……

Skin Prick & Intradermal Testing - Medications Version 1.0 02/09/2019

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Appendix 2: Dilution instructions

Amoxicillin 250mg		
Strength /formulation		250mg powder for injection
Skin prick test	**Concentration**	20mg/ml
	Dilution instructions	1. Reconstitute the 250mg vial with 5mls water for injection to give approx. 50mg/ml solution. 2. Withdraw 0.4mls and dilute with 0.6mls sodium chloride 0.9% to give a 20mg/ml solution
Intradermal test	**Concentration**	20mg/ml
	Dilution instructions	As above
Comments		If the specified formulation is not available then the dilution instructions will need to be amended accordingly. Once reconstituted products must be used immediately.
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

Amoxicillin 500mg		
Undiluted strength /formulation		500mg powder for injection
Skin prick test	**Concentration**	20mg/ml
	Dilution instructions	1. Reconstitute the 500mg vial with 10mls water for injection to give a 50mg/ml solution. 2. Withdraw 4mls (200mg) and dilute with 6mls sodium chloride 0.9% to give a 20mg/ml solution.
Intradermal test	**Concentration**	20mg/ml
	Dilution instructions	As above
Comments		If the specified strength and formulation is not available then the dilution instructions will need to be amended accordingly.
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

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Benzyl penicillin		
Strength /formulation		600mg powder for injection
Skin prick test	**Concentration**	6mg/ml
	Dilution instructions	1. Reconstitute the 600mg vial with 10mls water for injection to give 60mg/ml. 2. Withdraw 0.1mls (6mg) and dilute this with 0.9mls sodium chloride 0.9% to give a 6mg/ml solution
Intradermal test	**Concentration**	6mg/ml
	Dilution instructions	As above
Comments		If the specified formulation is not available then the dilution instructions will need to be amended accordingly. Once reconstituted products must be used immediately.
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

Appendix 2.1:

Co-amoxiclav		
Strength /formulation		1.2g, powder for solution for injection /infusion
Skin prick test	**Concentration**	20mg/ml
	Dilution instructions	1. Reconstitute with 20mls water for injections to give 50mg /ml 2. Withdraw 0.4mls (20mg) and dilute up to 1ml of sodium chloride 0.9% (to give 20mgs/ml)
Intradermal test	**Concentration**	20mg/ml
	Dilution instructions	As above
Comments		Note the concentration above (20mg/ml) only takes into account the amoxicillin component (not the clavulanic acid component) If the specified formulation is not available then the dilution instructions will need to be amended accordingly. Once reconstituted products must be used immediately
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

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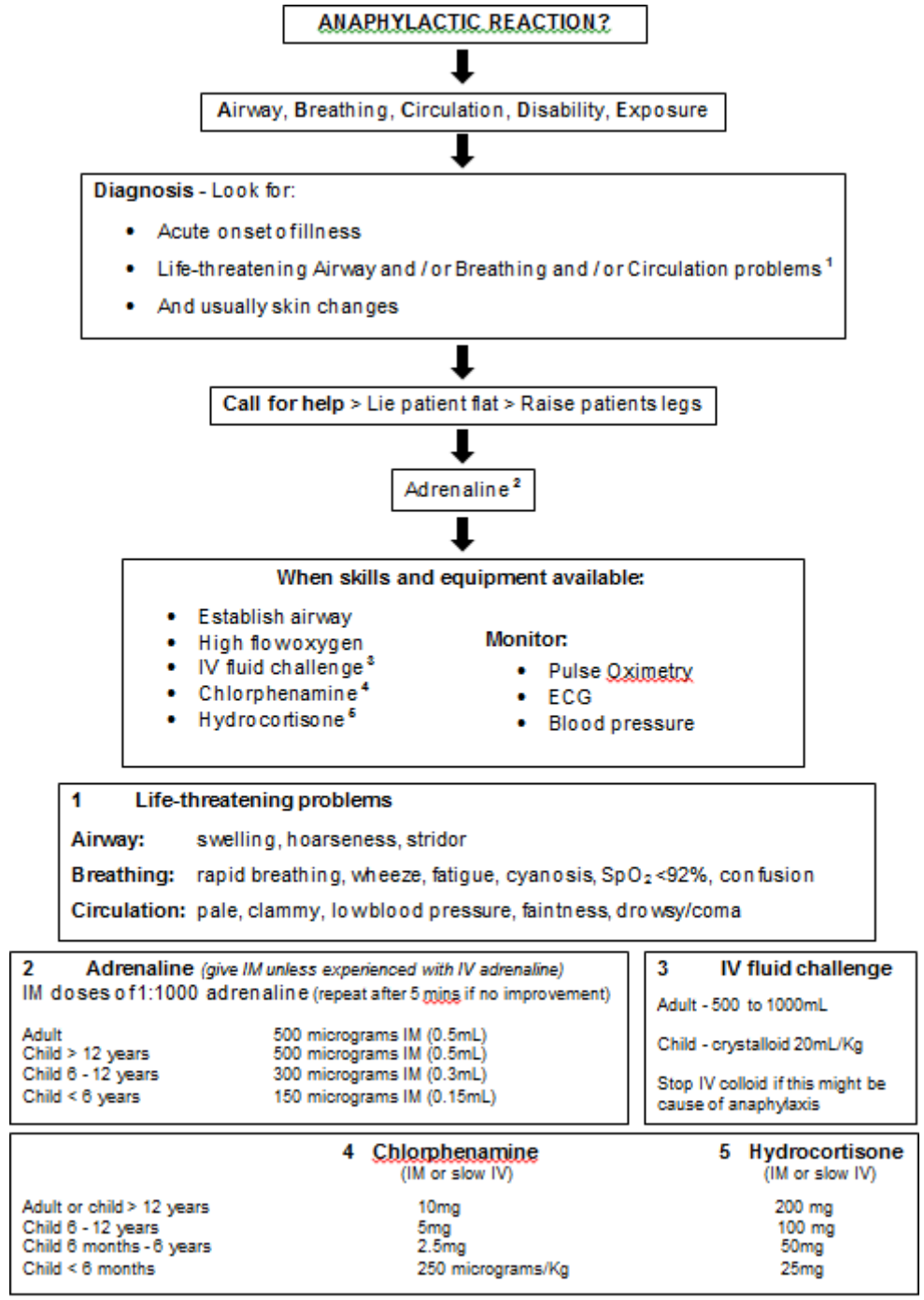
Flucloxacillin 250mg		
Strength /formulation		250mg, powder for solution for injection /infusion
Skin prick test	**Concentration**	20mg/ml
	Dilution instructions	Reconstitute with 5mls of water for injection to give 50mgs/ml. Withdraw 0.4mls (20mg). Then dilute up to 1mls with sodium chloride 0.9% to give 20mgs/ml
Intradermal test	**Concentration**	20mg/ml
	Dilution instructions	As above.
Comments		If the specified formulation is not available then the dilution instructions will need to be amended accordingly Once reconstituted products must be used immediately
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

Flucloxacillin 500mg		
Undiluted strength /formulation		500mg, powder for solution for injection /infusion
Skin prick test	**Concentration**	20mg/ml
	Dilution instructions	1. Reconstitute the 500mg vial with 10mls water for injection to give 50mg/ml 2. Withdraw 0.4mls (20mg) and dilute to 1ml with sodium chloride 0.9% (= 20mgs/ml)
Intradermal test	**Concentration**	20mg/ml
	Dilution instructions	As above
Comments		If the specified strength and formulation is not available then the dilution instructions will need to be amended accordingly.
References		Brockow, K et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013 Jun; 68(6):702-12. doi: 10.1111/all.12142. Epub 2013 Apr 25.

The Leeds Teaching Hospitals NHS
NHS Trust

Appendix 3



Reference: https://www.resus.org.uk/anaphylaxis/emergency-treatment-of-anaphylactic-reactions/ [Accessed 10 June 2019].

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Cross, S. (2007) Understanding skin prick testing, Nursing Times: online. Available at: https://www.nursingtimes.net/understanding-skin-prick-testing/199992.article [Accessed 14 May 2019].

Heinzerling et al. (2013) The skin prick test – European standards. Clinical and Translational Allergy. 3:3.

Bousquet et al (2012) Practical guide to skin prick tests in allergy to aeroallergens. Allergy 67: 18-24: Online. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1398-9995.2011.02728.x/pdf [Accessed 17 May 2019].

Toolan, J. (2008) Protocol for Skin Prick Testing. Department of Clinical Immunology and Allergy. Leeds Teaching Hosptals. Version 3.

Details of the electronic health record functions used to facilitate delivery of the trial

SystmOne electronic health record system was utilised to streamline trial processes and to deliver key functionality in the penicillin allergy assessment pathway[1].

Patient identification. Reports in functions were used to identify patient with a penicillin allergy record and who had received an antibiotic within the previous 24 months.

Secure access to patient data. An "ALABAMA unit" was set up in SystemOne into which consented research participants were referred. This allowed the research team to identify and contact new recruits for randomisation and baseline data collection. It allowed the team to follow-up participants. Reports were generated in the unit to identify participants who had received a recent prescription, so they could be assessed for primary events. Reports were also generated at the end of the trial to contribute trial outcome data.

In previous qualitative research we found that GPs were happy to update primary care medical records after a negative penicillin allergy test result if they were given clear directions. During interviews, GPs had expressed concerns that penicillin allergy records might easily be reinstated if the process was not managed properly. It was found that a penicillin allergy record in SystmOne could be removed in different ways – the process of updating records and how it was decided upon is described elsewhere[1].

[1]Ahmed S, Fielding J, Porter CE, et al. Utilising primary care electronic health records to deliver the ALABAMA randomised controlled trial of penicillin allergy assessment. *Trials* 2024; **25**(1): 653.

Primary Care
Clinical Trials Unit

STATISTICAL ANALYSIS PLAN

ALABAMA
ALlergy AntiBiotics And Microbial resistAnce

ALABAMA: **AL**ergy **A**nti**B**iotics **A**nd **M**icrobial resist**A**nce

Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance

Version 1.0

9 April 2024

VERSION HISTORY

Version:	Version Date:	Changes:
0.1	4 August 2021	Original version
0.2	28 April 2022	Updated contacted information for trial team. Removed the ADQ outcome Included additional exploratory analysis excluding participants recruited during COVID.
0.3	4 May 2022	Updated in inclusion/exclusion criteria and updated model used in the primary analysis to reflect the current version of the protocol. Updated safety analysis section with details regarding reporting of adverse events and adverse reactions.
0.4	19 May 2022	Explicated stated the family and the link function to use for the primary analysis. Including time in the study (years) to be adjusted for in the analysis models as participants recruited earlier will have a longer study duration and thus possibly higher re-prescription rates and hospital admission, or in the very least, more time in which these events can occur.
0.5	10 November 2022	Updated definition of the primary outcome
0.6	22 June 2023	Updated definition of the primary outcome
0.7	19 December 2023	Updated several sections of the SAP to align with version 13.0 of the protocol
0.8	19 February 2024	Updated the SAP to align with version 14.0 of the protocol and Ushma Galal's comments
0.9	26 February 2024	Updated the SAP in response to UG and NW comments
0.10	1 March 2024	Updated the SAP in response to UGs comments
0.11	15 March 2024	Updated the SAP in response to the trial teams comments from the meeting on the 11 March 2024. Sensitivity analysis regarding excluding participants recruited over COVID removed.
0.12	22 March 2024	Updated the SAP in response to UG and NW comments
0.13	22 March 2024	Corrected typo
0.14	5 April 2024	Responded to the CI comments
1.0	9 April 2024	Signed off

TABLE OF CONTENTS

1 INTRODUCTION

Trial title: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance

Short title: ALABAMA: Allergy antibiotics and microbial resistance

Ethics Ref: 19/LO/0176

Sponsor: University of Leeds

Funder: National Institute for Health Research (NIHR)

Protocol Data and Version No.: 16 November 2023, version 14.0

PREFACE

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PURPOSE AND SCOPE OF THE PLAN

This document details the proposed analysis of the main papers reporting results for the National Institute for Health Research (NIHR) funded randomised controlled trial to determine whether the PAAP intervention is clinically effective in improving antibiotic prescribing, patient outcomes and de-labelling. The results reported in these papers should follow the strategy described here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-point for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal and uploaded in advance of analysis to clinicaltrials.gov submission NCT04108637. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

Any deviations from this statistical analysis plan will be described and justified in the final report of the trial. This analysis should be carried out by an identified, appropriately qualified, and experienced statistician, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures.

TRIAL OVERVIEW

The importance of antimicrobial resistance (AMR) and the need to reduce its impact is well recognised (Davies 2013). Penicillins are the most commonly prescribed antibiotics (Public Health England 2017) and remain the first-line therapy for many common infections. A record of penicillin allergy has a marked effect on antibiotic prescribing (Solensky et al. 2000; Salkind et al. 2001; McLean-Tooke et al. 2011; Blumenthal et al. 2018; West et al 2019). Penicillin allergy records are common because side effects and symptoms related to the infection requiring antibiotic treatment are often mislabelled as allergies. About 6-10% of the UK population self-report a penicillin allergy but, importantly, fewer than 10% of these patients are truly allergic (NICE 2014; West et al 2019). Consequently, a significant proportion of the population are potentially restricted access to highly effective penicillins. Penicillin allergy records are associated with AMR; evidence from the UK and USA suggests that patients with a penicillin allergy record are more likely to acquire multi-drug resistant bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA) (Reddy et al. 2013; Macy & Contreras 2014; Blumenthal et al. 2018; West et al. 2019).

The focus of ALABAMA is 'false positive' records of penicillin allergy, how these affect prescribing and whether a complex intervention aimed at correcting inaccurate records is clinically/cost effective. Patients with a penicillin allergy are usually not prescribed penicillins but instead receive alternative, broad-spectrum antibiotics which may lead to suboptimal therapy, be associated with poorer longer-term outcomes, and contribute to AMR (Charneski et al. 2011; Currie et al. 2014; Blumenthal et al. 2018; West et al 2019). Our preliminary research found macrolide, tetracycline, cephalosporin, quinolone, and clindamycin prescribing were all more common in patients with a record of penicillin allergy compared to those without, and that antibiotic prescriptions were almost twice as frequent in patients with a penicillin-allergy record (West et al. 2019). These differences were not explained by age, sex, or comorbidity. Systematic review evidence indicates that antibiotic-allergies affect health outcomes, increasing mortality, length of stay, and costs (Krah et al 2021 (https://www.ncbi.nlm.nih.gov/pubmed/33059777). The large discrepancy between reported and true allergy rates suggests that introducing a *'pre-emptive'* penicillin allergy assessment pathway (PAAP) for patients who are more likely to receive antibiotics, could impact upon antibiotic prescribing, yield patient benefits, limit AMR/Healthcare associated infection (HCAI), and deliver NHS cost savings.

Assessment of patients with penicillin allergy in specialist clinics is already provided within the NHS, but most who are eligible are not offered the service because of a lack of capacity (Krishna et al. 2017). Currently, penicillin allergy testing in many immunology/allergy clinics is performed over at least two clinic visits; the first, to undertake history and perform skin testing (ST); the second to assess reactions and undertake oral challenge testing (OCT) followed by communication of results. The allergy history is important to determine if the allergy history is spurious, of uncertain risk, low risk, or high risk of true penicillin allergy (Krishna et al. 2014). Skin testing and OCT may follow.

The ALABAMA trial approach will be different from this standard NHS practice in two ways:

1) Streamlining the process by undertaking initial elements (history) in the community/via telephone, and developing a "one stop shop" single hospital clinic visit for assessment (skin testing and/or OCT)
2) Pre-emptive testing will be undertaken in patients with a higher risk of being prescribed antibiotics in primary care, rather than in the context of an acute allergic reaction or soon after a reaction

If the evaluation finds that this more 'patient-friendly' approach to allergy testing is more efficient, this would enable more patients to be tested within current resources. This proposed trial testing will take place in an hospital clinic but testing could be undertaken by appropriately trained staff in all units with facilities to deal with severe allergic reactions. It is important to note that pre-emptive allergy testing as outlined in the ALABAMA PAAP is different from testing a patient who has an absolute need for a penicillin to treat a life-threatening

infection. The risk-benefit analysis is different in these two situations and a more cautious approach has been taken in the ALABAMA PAAP.

PAAP has deliberately been designed as an efficient one-stop procedure that will involve [1] medical history in primary care to either [i] exclude those at risk of anaphylaxis or other severe adverse reactions, or [ii] indicate a referral to secondary care and [2] half a day in clinic and potentially a three-day post clinic course of oral antibiotics. The PAAP differs from current standard UK and European guidelines in that it offers patients assessed as 'low risk' of true allergy an abbreviated test consisting of direct oral challenge, with no preceding skin tests. Whilst the gold standard test with which to establish tolerance to penicillin is an oral challenge, current UK and European guidelines advise that patients should first be skin tested, using prick or intradermal tests, or both, although there is now recognition that this is not needed for lower risk patients (Savic et al 2022) (https://www.ncbi.nlm.nih.gov/pubmed/36128691). Skin testing identifies patients who are IgE-sensitised, and provides risk stratification for progression to a challenge test, for those with higher risk histories. Skin tests have a negative predictive value (NPV) approaching 100%, and patients who do not react to prick or intradermal tests are therefore unlikely to have a severe reaction on challenge. However, the interpretation of positive skin tests is less clear; these patients are generally not offered a challenge test and so the positive predictive value (PPV) is hard to determine. The PPV is generally accepted to be less than 50% based on a limited number of prospective studies, and on outcomes from accidental re-exposure. Increasingly, the evidence demonstrates that patients can be risk stratified for a challenge test on the basis of history alone. Where symptoms are not severe, not suggestive of an IgE-mediated reaction, are vague, or historic, the utility of skin testing is low and a direct oral challenge may be safe and appropriate. This approach is already used routinely for children in the UK and several studies have demonstrated safety and efficacy in adults. Patients whose histories are not clearly low risk will skill undergo skin testing, and only proceed to oral challenge if this is negative.

The PAAP will be divided into three stages which can initially be undertaken in a primary care setting but move to a hospital clinical setting for more complex testing. Each stage has been risk assessed based on published data and expert opinion to minimise risk of harm and keep the costs of the pathway down.

OBJECTIVES

All the study objectives are described below. A full summary of the study objectives and outcome measures can be found in Appendix I (section 0), and the current version of the protocol (version 14.0).

1.1.1 PRIMARY OBJECTIVE

The primary objective is to determine the effect of PAAP on penicillin prescribing.

1.1.2 SECONDARY OBJECTIVES

1) To determine whether the PAAP intervention is clinically effective in improving treatment response failure,
2) Effects of PAAP on symptom duration,
3) Effects of PAAP on total antibiotic prescribing,
4) Effects of PAAP on hospital admissions and length of hospital stays (safety outcomes),
5) Effects of PAAP on mortality rates (safety outcome),
6) Effects of PAAP on Meticillin-resistant *Staphylococcus aureus* (MRSA) infection/colonisation,
7) Effects of PAAP on *Clostridioides difficile* infection,

8) To explore patient and clinical views and experiences of penicillin allergy testing, test results, and future antibiotic use,
9) (Process evaluation) To explore patient and clinician experiences of trial procedures,
10) To measure the influences on clinician and patient behaviour change regarding prescribing and consuming penicillin following a negative test result,
11) Cost effectiveness for the PAAP intervention compared to usual care,
12) Effects of PAAP on de-labelling:
    a) at 3 months post randomisation,
    b) up to 12 months post randomisation.
13) Additional safety outcomes (exploratory outcome)
14) Effects of PAAP on all outcomes for follow up post 12 months.

N.B. Objectives 8, 9, 10, and 11 will be analysed as part of the qualitative, economic, and process evaluation and will be reported separately from the main statistical analysis report.

2 TRIAL DESIGN

This is a multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested pilot trial.

Potential participants who met the eligibility criteria were identified during a search of their electronic health records at their general practice. The electronic search criteria were developed centrally by the research team in partnership with TPP and made available for running locally on SystmOne e.g. by practice managers, Local Clinical Research Network (LCRN) Research Nurse Team, or Leeds CCG Pharmacy Technician team. Potential participants were sent an invitation pack and those interested in taking part returned an expression of interest form to the trial team. They were telephoned and booked into an either a face to face, or telephone appointment with their GP or Research Nurse at a time that was convenient to them. During this appointment, their GP or a delegated member of the staff confirmed their eligibility to participate and consented them to take part in the trial. The participants then received another telephone call from a member of the trial team to complete the baseline case report form (CRF). At this point, the participants were asked if they had taken any antibiotics in the previous two weeks; if they had, the randomised/baseline call will be postponed until the participant has been free of antibiotic use for two weeks.

Once the baseline CRF was complete the participants were randomised to usual care or the PAAP intervention arm. Those randomised to the PAAP intervention arm were booked into an appointment at the clinic where they had penicillin allergy testing.

Participants recruited during the nested pilot phase were followed up for an initial 4 months for the feasibility outcomes, during which they were contacted monthly by the trial team. Following a “stop go” assessment, all nested pilot study participants were subsequently followed up for at least 12 months in the main trial to align their follow-up with participants recruited to the main trial.

Regular reports were run in the ALABAMA unit to identify participants who had been prescribed an antibiotic, for any cause, in the previous 7 days. A member of the research team sent an alert to the trial research nurses team who then followed the participant up for the duration of the associated infection. The research team then designated an antibiotic prescription as a ‘primary event’ if the patient was prescribed an antibiotic for a pre-defined list of infections (see Appendix II). Participants receiving antibiotics for a primary event, were asked to complete a symptom diary. At the end of the follow up period their electronic health records were reviewed to ensure we had captured all antibiotic events. All trial participants had case note review and, if required had capture hospital episode statistics, and mortality data.

Throughout this process general practice staff and participants received behaviour change intervention materials.

See Appendix III for study flowchart.

OUTCOME MEASURES

A summary of the study objectives can be found in section 0. An outline of the trial procedures and time points can be found in Appendix IV. Only the outcomes which pertain to this statistical analysis plan will be listed here.

2.1.1 PRIMARY OUTCOME – EFFECTS OF PAAP ON PENICILLIN PRESCRIBING

The primary outcome is the effect of PAAP on penicillin prescribing, and is defined as: the proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (see Appendix II) up to 12 months post-randomisation.

The primary outcome will be coded as 1 ("Yes") if there is evidence of a penicillin prescription during the course of routine care, up to 12 months post randomisation on any of the following data sources: SystmOne report/notes review (Variable *ISPRIMARYEVENT*), patient follow-up calls, or hospital prescribing reports. Participants that have not required penicillin treatment during the trial will have their primary outcome coded as 0 ("No").

Participants who do not have evidence of a prescription and who withdrew consent for notes review to be conducted, will have their primary outcome missing at 12 months.

2.1.2 SECONDARY OUTCOMES

2.1.2.1 TREATMENT "RESPONSE FAILURE"

Treatment "response failure" defined as: re-presentation with worsening or non-resolving or new symptoms (related to the index infection) 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 (collected from the SystmOne report, patient symptom diaries, and post antibiotic telephone call). Treatment "response failure" will be coded as 1 ("Yes") if the patient went back to the GP because symptoms worsened, or if the symptoms did not resolve, or if new symptoms developed, this information is collected from the symptom diary. This outcome will also be coded as 1 ("Yes") if the participant had a new antibiotic prescribed on the day 28-30 post antibiotic telephone call (Variable *REPRESCYN*) for the same index condition, or if there is evidence of a re-prescription on the SystemOne report and this was confirmed as a treatment response failure on notes review. Participants who have no evidence of a treatment "response failure" on any of these data sources, will have this outcome coded as 0 ("No"). Participants who withdrew before 12 months with no prescription event and who withdrew consent for notes review to be conducted will have this outcome missing.

2.1.2.2 Duration of symptoms rated 'moderately bad' or worse

The predominant symptoms are scored daily on a scale from 0 to 6 (0 = no problem, 1 = very little problem, 2 = slightly problem, 3 = moderately bad, 4 = bad, 5 = very bad, and 6 = as bad as it could be). The scale is taken from a validated measure (Watson et al. 2001). The duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment will be derived from the day 1-28 symptom diary question "*Tell us how bad these symptoms are today by ticking the box for your chosen number that fits best with how you are feeling*" which is completed after each antibiotic prescription. The number of days the patient answered, "moderately bad" (score = 3), "bad" (score = 4), "very bad" (score = 5), or "as bad as it could be" (score = 6) for the first antibiotic prescription event from the diaries will be calculated.

If the patient did not complete all their symptom diaries the day 28-30 post antibiotic telephone call will be used. At the day 28-30 call, participants are asked if their symptoms have resolved, and if they did resolve, how many days did it take for the symptom to become a minor problem or less (Variables *SYMPT1RESLV SYMPT2RESLV SY1RESLVNUM SY2RESLVNUM*). If the patient indicated on the call that the symptom did not resolve this outcome will be coded as 28 days.

If a patient had a prescription event that required diary completion, but they did not fill out any diaries or complete the 28-30 call this outcome will be missing.

2.1.2.3 Antibiotic prescriptions

There are three outcomes related to antibiotic prescriptions for pre-defined infections throughout the trial. Information regarding antibiotics will be obtained from the 12 months notes review, the SystmOne reports, and the post antibiotic telephone call. The outcomes of interest are:

1) Antibiotic usage in terms of number of prescriptions,
2) Number of days of treatment,
3) Defined daily dose (DDD),

Each outcome will be calculated separately for all antibiotics of interest, and split by antibiotic type (penicillin, and non-penicillin) as well as antibiotic class (see spreadsheet: K:\ID\ALABAMA\STATS\2. Stats Plan and Sample Size\SAP\ABX categories & DDD for analysis_07Aug2023.xlsx). A list of the pre-defined infections of interest can be found in Appendix G of the protocol, and Appendix II of this document. Long term antibiotic prescriptions, defined as periods of continuous use for ≥3 months used for prophylaxis or "anti-inflammatory" indications will be excluded from the analyses.

2.1.2.3.1 Number of Antibiotic prescriptions

This outcome will be derived from the notes review question "*Please list all the antibiotics the patient was treated with for the above event or symptoms*" (Variable *ABXNAME*), as well as data from the SystmOne report and hospital prescribing report (if available). This outcome will be derived as the number of antibiotic prescriptions up to 12 months post-randomisation. If there is no evidence of antibiotic usage this outcome will be coded as zero. A "prescription" will be considered to be an uninterrupted period of antibiotic use. Where a period of at least 2 days separates prescriptions for the same antibiotic, these will be considered separate prescriptions.

If the patient had a relevant infection event but there is no prescription data for that patient then this outcome will be missing. Patients who also withdrew before 12 months who do not have an antibiotic prescription, and who withdrew consent for notes reviews to be conducted will also have this outcome missing.

2.1.2.3.2 NUMBER OF DAYS OF TREATMENT

This outcome will be derived from the start and stop dates across the different data sources: the SystmOne report and the notes review (Variables *ABXPRESTARTDAT, ABXPRESTOPDAT*) and hospital prescribing report. The total number of days the participant was taking antibiotics for each prescription event will be added to give the total days prescribed antibiotic treatment for the 12-month period. This will be calculated as the stop date minus the start date plus one, if there is no evidence of antibiotic usage this outcome will be zero. If a patient has the antibiotic usage outcome (above) missing, then this outcome will also be missing.

2.1.2.3.3 DEFINED DAILY DOSE (DDD)

This outcome will be derived from the notes review question "*Dose*" (Variable *ABXDOSE*) and *"Units"* (Variable *ABXUNITS*), as well as the SystmOne report and hospital prescribing report. The doses will need to be standardised into grams before DDD can be calculated. Each participants' defined daily dose will be calculated using the formula (Total dose in grams * Total treatment duration) / DDD factor, if there is no evidence of antibiotic usage this outcome will be zero. If a patient had the antibiotic usage outcome (above) missing, then this outcome will also be missing.

2.1.2.4 HOSPITAL ADMISSIONS

Information regarding hospital admissions will be obtained from the HES data, post antibiotic day 28-30 telephone call, and the notes review. This outcome will be derived as:

i) A binary variable (yes/no) if there is any evidence that the participant had a hospital admission in the 56 days after the start of a primary event, during the 12 months post-randomisation,

ii) The number of hospital admissions in the 56 days after the start of a primary event, during the 12 months post-randomisation. If there is no evidence of hospitalisation this outcome will be zero,

iii) The total number of days of hospitalisation in the 56 days after the start of a primary event, during the 12 months post-randomisation. If there is no evidence of hospitalisation this outcome will be zero.

Outcomes above only apply to admissions in the 56 days after start of a primary event, an exploratory analysis will also be conducted for all admissions during the 12 months post-randomisation.

2.1.2.5 MORTALITY RATES

Information regarding mortality will be obtained from the 12-month combined notes review question "*Is the participant alive?*" (Variable *ISALIVE*), the SAE report (Variable *SAESER*), the HES database, the ONS database, and the SystmOne report. This outcome will be derived as a binary variable and will be coded as affirmative if there is evidence of death on any of the sources listed above, this outcome will be coded as negative if there is no evidence of death on any of these sources. If there is a contradiction between the sources the participant will be assumed to have died. If a participant had withdrawn consent to note review/follow-up and there is no evidence of a death prior to withdrawal, then this outcome will be missing.

2.1.2.6 MRSA INFECTION/COLONISATION

Whether or not a participant acquired a MRSA infection up to 12 months after randomisation will be obtained from the notes review at 12 months (Variable *MRSAYN*), as well as the SystmOne report.

2.1.2.7 *CLOSTRIDIOIDES DIFFICILE* INFECTION

Whether or not a participant contracted a *Clostridioides difficile* infection up to 12 months after randomisation will be obtained from the notes review at 12 months (Variable *CLSTDMYN*), as well as the SystmOne report.

2.1.2.8 DE-LABELLING AT 3 MONTHS POST RANDOMISATION

The proportion of ALABAMA participants whose labels are removed from the primary care medical electronic health record allergy section at 3 months post randomisation. This will be derived as affirmative if the participant was de-labelled on the de-labelling CRF (Variable *DELABELLEDYN*) and this occurred within 3 months (90 days) from randomisation (Variable *DELABELDAT*). Otherwise, this outcome will be negative. Participants who were not de-labelled within 3 months and withdrew consent for notes reviews to be conducted will have this outcome as missing.

2.1.2.9 DE-LABELLING AT 12 MONTHS POST RANDOMISATION

The number and proportion of ALABAMA participants whose labels were removed (delabelled) by 3 months post randomisation and the number/proportion of ALABAMA participants who were delabelled the primary care medical electronic health record up to 12 months post-randomisation. This outcome will be derived similar to the outcome above and will be classed as affirmative if the participant was de-labelled within 12 months (365 days) and were not relabelled (Variable *RELABELLED*). Separately, the number of trial participants who were relabelled after being delabelled, in each arm will be reported.

TARGET POPULATION

Participants who were over 18 with a record of a penicillin allergy.

2.1.3 INCLUSION CRITERIA

- Participant was willing and able to give informed consent for participant in the trial,
- Male or Female, aged 18 years or above,
- Current penicillin allergy (or sensitivity) record of any kind in their primary care electronic health record,
- Prescribed systemic antibiotics, either: penicillin, cephalosporin, tetracycline, quinolone macrolide, glycopeptide, aminoglycoside, oxazolidinone, monobactam, or carbapenem class antibiotic, or fosfomycin, nitrofurantoin, trimethoprim, clindamycin, rifampicin, colistin, metronidazole in the previous 24 months.

N.B.1 Patients who had been formally tested for penicillin allergy in the past and were found not to be penicillin allergic but still has a medical record indicating a penicillin allergy, were eligible for the trial.

2.1.4 EXCLUSION CRITERIA

The participant may not enter the trial if ANY of the following applied:

- Life expectancy estimated <1 year by GP,
- Unable to attend hospital clinic where allergy testing takes place,
- Unsuitable for entry into testing pathway because:
    - Allergy history consistent with anaphylaxis to penicillin,

- History of toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) or any severe rash which blistered or needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin,
- Has been formally tested for penicillin allergy in the past and been found to be penicillin allergic,
- History of brittle/severe asthma or has had a course of steroids in the past 3 months for asthma or unstable coronary artery disease, or other severe/poorly controlled skin conditions,
- Or considered unsuitable for trial participation by the GP e.g. because of chaotic lifestyle.

- Pregnant,
- Breastfeeding mothers,
- Currently taking beta blocker medication, and unable to temporarily withhold these on the day of penicillin allergy testing,
- Currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pre-testing,
- Or currently taking antihistamines and unable to temporarily withhold these for 72 hours pre-texting.

GPs may have also wanted to exclude vulnerable patients who were deemed to be unsuitable to participate for other reasons such as, but not limited to, terminal illness, reliability, mental illness, learning difficulties, anxiety, other family circumstances.

N.B.1 Patients that were currently taking medicines with antihistamine properties that cannot be temporarily withheld or patients with isolated dermographism may still have be eligible to participate but this needed to be discussed with the research team prior to consent.

N.B.2 Pregnancy and breastfeeding exclusion criteria was only applicable at screening (due to potential risks of PAT); these patients would not need to be withdrawn if in follow up.

SAMPLE SIZE

The primary outcome was initially treatment response failure defined as the percentage of re-prescription of an alternative antimicrobial within 28 days of an index prescription. A total sample size between 1592 and 2090 participants provided 80-90% power to detect a clinically important absolute difference of 7.9% in re-prescription rate at one year between groups (i.e. reducing from 19.8% in the control group to 11.9% in the PAAP group) at 5% level of significance (2-sided). The sample size had been adjusted assuming 50% of participants will require at least one prescription within 1 year from randomisation and allowing for 10% dropout. Participants are classed as enrolled at the point of randomisation.

The primary outcome was then changed to ‘effects of PAAP on penicillin prescribing’, defined as ‘The proportion of participants who receive prescriptions for a penicillin attending for predefined conditions where a penicillin is the first-line recommended antibiotic (see Appendix II) during the course of routine primary care up to 12 months post randomisation. A total sample of 848 (i.e. 424 per group) was required to provide 90% power to detect an increase in the proportion of penicillin prescription from 4% (Usual Care) to 14% (PAAP) over the year after randomisation at 5% level of significance (2-sided) and 10% attrition. The sample size has been adjusted assuming 50% of participants will require at least one prescription within 1 year from randomisation. At 80% power, the sample size required was 656 (i.e. 328 per group). The table below also provides the sample size required if not all participants have reached 12 months follow-up.

Power	% Difference	Total sample size (all reached 12 months FU)	Total sample size (80% reached 12 months FU)	Total sample size (90% reached 12 months FU)
80%	10%	656	820	729
	15%	372	465	413
90%	10%	848	1060	942
	15%	472	590	524

Results from our recent analysis, using data extracted from the SystmOne database, suggested that there were an average of 110 patients per average practice size of 6000 who fulfilled our inclusion criteria.

1) Adults (over 18 years),
2) Penicillin allergy in electronic health records,
3) And in receipt of a penicillin, cephalosporin, tetracycline, quinolone, or macrolide class antimicrobial in the previous 24 months.

Not all patients will have an eligible antibiotic prescription for an infective episode during the follow-up period, and not all episodes will generate analysable data. We have allowed for 50% patients not contributing any data to the primary outcome.

RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

During their call with the research team, participants were asked if they had taken any antibiotics in the previous two weeks; if they had, the randomisation/baseline call was postponed until the participant was free of antibiotic use for two weeks. The research team arranged another call to take place when the participant had been free of antibiotic use for two weeks. During the call, the participants were asked to complete the baseline assessment and the member of the research team performed randomisation. Randomisation was performed using Sortition (PC-CTU's in-house online randomisation system) according to the current version of the SOP PC-CTU_SOP_IT104. Allocation was minimised by general practice, age, number of antibiotic prescriptions up to 24 months prior to randomisation, and number of Quality Outcome Framework registered diseases, to ensure balance of allocation of these baseline covariates. Patients were randomised to either usual care (with subsequent monitoring for antibiotic prescriptions and follow-up for trial outcomes as determined by the clinical indication for antibiotics) or the PAAP intervention arm using an allocation ratio of 1:1. Both the participants and the recruiter knew which arm they were randomised into. The trial statistician will remain blinded to treatment allocation when performing the final analysis. Unblinding of the allocation will take place in accordance with SOP PC-CTU_SOP_ST105.

N.B. Patients randomised to the PAAP trial arm, who do not attend an appointment for PAT, will continue to be followed up unless consent is withdrawn.

NOTE: There have been some errors made during the randomisation procedure, at least one participant's minimisation data has been entered incorrectly onto Sortition (and cannot be corrected). As such, the information collected on the baseline CRF (data from OpenClinica) will be used as covariates in the analysis regardless of the information that was used for the randomisation. Information from both the baseline CRF and the information used in the randomisation (Sortition) will be presented in the baseline table.

3 ANALYSIS – GENERAL CONSIDERATIONS

DESCRIPTIVE STATISTICS

Frequencies (with percentages) for binary and categorical variables, and means (with standard deviations), or medians (with lower and upper quartiles), and the range (minimum and maximum values) for continuous variables will be presented by randomised arm.

CHARACTERISTICS OF PARTICIPANTS

The following baseline characteristics of participants from the baseline questionnaire and the baseline TPP form will be presented by randomised arm and overall (also see dummy table in Appendix V):

- Age (means and standard deviations, randomisation categories (from Sortition), and according to SOP ST101_v4.0 (based on EudraCT guidelines) as adults 18-64 years, adults 65-84 years and adults 85 years and over),
- Gender,
- Ethnicity (collected from the notes review CRF),
- Index of multiple deprivation quintiles (IMD) (will be derived from a list of postcodes provided by the trial manager),
- Number of antibiotic prescriptions in the 24 months prior to recruitment (from both Sortition and TPP) (12 months for those recruited to the nested pilot study)
- Number of QOF registered diseased (from both Sortition and TPP)
- Other information from SystmOne (Antibiotic prescriptions in the 12 months prior to recruitment, and 12-24 months prior to recruitment, and number of participants with each each QOF registered disease).
- Patient reported penicillin allergy history (how long has the participant been allergic to penicillin, the name of the penicillin that cause the allergic reaction, how was the penicillin that caused the allergic reaction taken, allergic symptoms, how long after taking penicillin did the participant get the allergic reactions, did the participant consult a doctor or attend an emergency department, was the participant admitted to hospital, does the participant have an allergic reaction to another group of antibiotics)
- Patient reported other significant medical history (does the participant have any other medical conditions, pregnant or breast feeding, currently taking any antihistamines, taken steroids within the last 10 days, taking any other medication either prescribed by GP or bought over the counter),

There will be no tests of statistical significance nor confidence intervals for differences between randomised groups on any baseline variables reported.

Participant throughput from screening through randomisation, follow-up, and analysis will be presented in a flow diagram, and include reasons for withdrawal (see Appendix VI).

DEFINITION OF POPULATION FOR ANALYSIS

The primary analysis population will include all randomised patients in the treatment arm they were assigned to, regardless of treatment received. All data will be included in the analysis as far as possible, though there will inevitably be the problem of missing data due to withdrawal, loss to follow-up, or non-response to questionnaire items.

Participants withdrawn for post-randomisation ineligibility will be excluded from the analyses. Those randomised but who were not eligible at the PAAP clinic will not be included in the analysis population. Those who were eligible but decided not to go ahead with PAAP will be included in the analysis population.

The primary analysis will also be carried out on the "as treated" (AT) analysis population. All participants who were allocated to PAAP and had exposure to the test (i.e., they completed either the skin test or oral challenge test, or both), will be included in the as-treated PAAP arm. Those participants who were randomised to PAAP but did not have a test or who were randomised to usual care will be included in the usual care arm.

POOLING OF INVESTIGATIONAL SITES

Analysis will not be pooled as the primary and secondary analysis sufficiently account for the different centres.

For the primary and secondary analyses, the models are adjusted for site as a random effect. Sites that have less than 5 participants will be grouped into an 'other' category for the purpose of the analyses.

DATA MONITORING COMMITTEE AND INTERIM ANALYSES

A Data Monitoring Committee (DMC) was appointed in line with standard CTU procedures. The responsibility of the group is to assess the data at each interim review, as the updates to the randomisation scheme occur in order to ensure that the process is working correctly and to review and monitor the accruing data to ensure the rights, safety, and wellbeing of the trial participants. They will make recommendations to the Trial Steering Committee (TSC) about how the trial is operating, any ethnical or safety issues and any data being produced from other relevant studies that might impact the trial.

All DMC reports can be found on the PC-CTU restricted drive "K:\ID\ALABAMA\STATS\4. TSC and DMC\DMC"

No interim analysis for efficacy was planned for this study.

4 PRIMARY ANALYSIS

The primary objective is to determine whether the PAAP intervention is clinically effective in improving antibiotic prescribing.

PRIMARY OUTCOME

The primary outcome is penicillin prescribing, defined as the proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic up to 12 months post-randomisation. A binomial mixed-effects generalised linear model (MEGLM) with a logit link function will be fitted to the data with penicillin prescribing within 12 months of randomisation, as the dependent variable. The model will include randomised group, age, number of antibiotic prescriptions (as a continuous variable) up to the 24 months prior to randomisation (up to 12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects. These variables will come from the clinical database. GP practice will be included as a random effect. The adjusted relative risk between the randomised groups and the corresponding 95% confidence intervals will be obtained from the marginal adjusted relative risk (based on delta-method standard errors (Norton et al. 2013)) between the randomised groups and reported alongside the associated P-value.

HANDLING MISSING DATA

Missing data will be reported, with reasons where available. The mixed effects regression model assumes data is missing at random (MAR), however the mechanism of missing data will be explored. The baseline characteristics listed in section 0 (except those that were patient reported, and the ones from Sortition used in the randomisation) will be summarised for both randomised groups, split depending on if the primary outcome is available or missing. A logistic regression model will explore any association between each baseline characteristic and the availability of the primary outcome. Covariates found to be predictive of missingness ($P<0.05$) will be included in the analysis model in a sensitivity analysis of the primary outcome (see section 6). If the primary outcome is available for all participants this will not be conducted.

Should any covariates (to be included in the model) have missing baseline data, the overall mean of the covariate at baseline will replace the missing values (Sullivan et al. 2018) to enable all randomised participants with outcome data to be included in the analysis.

HANDLING OUTLIERS

The primary outcome is a binary outcome collected from the notes reviews and the SystmOne database and hospital prescribing report, as such there is no expectation that there will be outliers.

MULTIPLE COMPARISONS AND MULTIPLICITY

This is a two-arm trial with one primary outcome which is clearly stated in the protocol. Thus, no adjustment for multiple comparisons is necessary. An effect will be interpreted as significant if the P-value is below 0.05.

5 SECONDARY ANALYSIS

BINARY OUTCOMES

The binary secondary outcomes:

- Treatment "response failure",
- Hospital admission,
- Mortality rates,
- MRSA infection/colonisation,
- *Clostridioides difficile* infection,
- De-labelling at 3 months post randomisation (to be analysed in the as treated population),
- And de-labelling up to 12 months post randomisation (to be analysed in the as treated population)

will be analysed using a binomial mixed-effects generalised linear model with a logit link function. The models will include randomised group (as treated group for the de-labelling outcomes), age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects. GP practice will be included as a random effect. The adjusted relative risk between the randomised groups and the corresponding 95% confidence intervals will be obtained from the marginal adjusted relative risk between the randomised groups and reported alongside the associated P-value.

If it is possible that the de-labelling outcomes could unblind the report, the summary statistics will not be presented in the blinded reported, only the treatment effects will. In this case, the summaries will only be presented in the unblinded report, once the blinded report is signed off. If there is insufficient data to compare the treatment groups, no formal analysis will be carried out and only summary statistics will be presented.

CONTINUOUS OUTCOMES

The continuous secondary outcomes:

- Duration of symptoms rated 'moderately bad' or worse,
- Number of days of antibiotic use (total and split by penicillin and non-penicillin, and antibiotic class)
- Defined daily dose (DDD) (total and split by penicillin and non-penicillin and antibiotic class),
- And length of hospital stays,

will be analysed using a linear mixed effects regression model. The models will include randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects. GP practice will be included as a random effect. The adjusted mean difference between the randomised groups with 95% confidence intervals and P-values will be reported.

The proposed analyses assumes that these secondary outcomes satisfy the assumptions of the linear mixed effects regression model. Histograms of the distribution of each outcome split by randomised group, and post estimate plots of the residuals will be presented. If the post estimate plots show evidence that the assumptions of the linear mixed effects regression model have been violated, transformation of the data will be attempted. If there is still evidence that the assumptions have been violated a quantile regression will be implemented. The quantile regression will include randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), number of QOF registered diseases, and GP practice as covariates. The adjusted median difference between the randomised groups with

95% confidence intervals, and P-values will be reported. If the quantile regression does not converge an unadjusted quantile regression will be attempted; if the model still does not converge a non-parametric approach such as a Mann-Whitty U test will be adopted.

Defined daily dose (DDD) split by class, is expected to be small for some classes in each randomised arm. If it is judged to be too small this will only be presented descriptively.

COUNT OUTCOMES

The count secondary outcomes:

- Number of antibiotic prescriptions (total and split by penicillin and non-penicillin, and antibiotic class),
- Number of hospital admissions (within 56 days of primary event onset), and 12 months

will be analysed using a Poisson mixed effects regression model. The models will include randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects. GP practice will be included as a random effect. The adjusted incidence rate ratio between the randomised groups with 95% confidence intervals, and P-values will be obtained from the model.

If there are excess zeros and/or over dispersion in the data, the Poisson model will the run with robust standard errors. If the model fails the converge, a zero-inflated Poisson model and/or a negative binomial model will be considered to analyses these outcomes.

Number of antibiotics split by class is expected to be small in some antibiotic classes in each randomised arm. If it is judged to be too small this will only be presented descriptively.

6 SENSITIVITY ANALYSIS

Sensitivity analyses will be conducted with respect to the primary outcome only (unless explicitly stated, see 6.6) and will explore the sensitivity of results departure from the randomisation policy, missing data, and the effect of the COVID-19 pandemic.

AS TREATED (AT)

Participants were analysed in their randomly assigned intervention arm for the primary analysis regardless of whether they received the intervention or not. A sensitivity analysis will be conducted analysing participants depending on whether they received the allocated intervention or not. The definition of the “as treated” (AT) analysis population is described in section 0.

The model used in the primary analysis (section 0) will be re-run on the AT group, with age, number of antibiotic prescriptions in the 24 months (12 months for those recruited to the nested pilot study) prior to randomisation, and the number of QOF registered diseases as fixed effects. GP practice will be included as a random effect. The adjusted relative risk between the AT groups and the corresponding 95% confidence intervals will be obtained from the model and reported alongside the associated P-value.

FACTORS THAT PREDICT MISSINGNESS

A logistic regression analysis, described in section 0 will be conducted to investigate factors (if any) that are predictive of non-response of the primary outcome. If any factors are associated with non-response, the model used in the primary analysis (section 0) will be re-run with these factors included in the model as fixed effects, alongside randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. The adjusted relative risk between the randomised groups and the corresponding 95% confidence intervals will be obtained from the model and reported alongside the associated P-value.

EXCLUDED PARTICIPANTS WHO DID NOT HAVE COMPLETE FOLLOW-UP

Participants recruited towards the end of the recruitment period may not have been followed-up for the full 12 months of the planned follow-up period. If there are any participants who were not followed-up for 12 months, the primary analysis (section 0) will be re-run with these participants excluded from the analysis.

EXCLUDING PARTICIPANTS WHO HAD DELAYED PAAP

There may be cases were a participant who was randomised to PAAP did not receive PAAP for quite some time. The primary analysis (section 0) will be re-run with the participants who were delayed in receiving the PAAP by more than 3 months (90 days) excluded from the analysis population.

7 SUBGROUP ANALYSES

No subgroup analysis was planned for in the protocol; however, the trial team suggested 3 subgroups of interest:

i) Age (<65 years versus ≥65 years),
ii) Number of QOFs at baseline (<2 versus ≥2),
iii) And IMD (split at the median).

The primary analysis (see section 0) will be rerun with an additional two-way interaction between randomised group and subgroup as a fixed effect. The adjusted relative risk between the randomised groups in each level of the subgroup and the corresponding 95% confidence intervals will be obtained from the model which will be reported alongside the associated P-value for the interaction. The results of the subgroup analyses will be presented in a forest plot.

8 EXPLORATORY ANALYSIS

The analysis for the hospital outcomes described above (hospital admissions, number of hospital admissions, and length of hospital stay) in the 56 days following a primary event will be reconducted for all hospital admissions during the 12 months trial period. This analysis should be considered exploratory.

9 SAFETY ANALYSIS

All participants randomised will be included in the safety analysis. The safety analysis will be conducted on an as treated (AT) basis, participants will be analysed by the intervention they actually received instead of the intervention they were randomised to receive. The safety analysis will be conducted on the AEs and SAEs as appropriate.

Safety of the trial participants is paramount. Consequently, PAAP testing is performed in a hospital clinic to mitigate any risk of dealing safety and swiftly with anaphylaxis or other serious reaction to the oral challenge test, this is standard care in hospital clinics where suitably qualified and trained personal and equipment are at hand. Access details to the on-call immunology staff are given to all participants as is this standard of care for all penicillin-allergy assessments to ensure appropriate management of problems that might develop after the participants return home.

Telephone calls by the research team at the following time-points collected information on adverse events (AEs) associated with the penicillin allergy test (skin test and/or oral challenge test): 4-6 days, and 28-30 days after penicillin allergy testing.

Adverse events occurring up to 28 days after an antibiotic prescription from their general practitioner for any pre-defined infections listed in the protocol is captured through the participant diary and telephone calls by the research team after the start of an antibiotic prescription.

The frequency of adverse events (AEs) and adverse reactions (ARs) will be summarised. A list of all adverse events and reactions experienced during the trial will be presented including information on the type of event, AE description, start date of AE, end date of AE, severity of the event, outcome of the AE, event related to treatment, what the adverse reaction was too, description of AR, what test the participant had (skin/OCT/both), and whether or not the participant went on to be de-labelled as being allergic to penicillin. Participants that went on to be de-labelled will be highlighted in the table of adverse events.

In addition to summarising all adverse events and reactions, only those that occurred during 3 days post antibiotic follow-up will be presented.

If the list and description of the adverse events could potentially unblind the report, this will not be presented in the blinded version of the report, only the summary statistics will be provided. In this case the detailed list of adverse events will only be presented in the unblinded report, which will only be prepared when the blinded report has been signed off.

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity,
- Or consists of a congenital anomaly or birth defect.

Other important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

- Anaphylaxis to an antibiotic will be considered an SAE as part of the ALABAMA trial.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

The number and percentage of participants experiencing at least one SAE will be reported by the intervention they received (rather than the intervention they were randomised to receive) and will be analysed using a Fisher's Exact test if possible. The total number of SAEs per AT group will be reported for each serious adverse event. The total number of SAEs per AT group will also be reported.

Any SAEs identified during the ALABAMA trial need to be assessed for their relatedness to:

1. Penicillin Allergy Assessment (PAA)

2. An antibiotic prescription* for any of the pre-defined infections listed in Appendix G of the protocol and Appendix II of this document.

*Because patients may have more than one antibiotic prescription during the ALABAMA trial, the relatedness of SAEs was assessed in relation to their most recent antibiotic prescription for any pre-defined infections.

SAE description, start date of SAE, stop date of SAE, severity of the event, reason the event was classified as serious, event related to intervention, was the event unexpected, outcome of the SAE, allocated intervention group, and received intervention, will be reported for each serious adverse event.

If the list and description of the serious adverse events could potentially unblind the report this will not be presented in the blinded version of the report. In this case the detailed list of serious adverse events will only be presented in the unblinded report, which will only be prepared when the blinded report has been signed off.

10 DESCRIPTIVE ANALYSIS

Objective 14 – Effects of PAAP on all outcomes for follow-up past 12 months (see Appendix I) will be conducted as part of the exploratory analysis. This will be presented descriptively, and the results may be provided in a separate report, as to not delay the dissemination of the main trial outcomes.

The principle of the descriptive analysis is that if PAAP is beneficial, it is likely to have a sustained/prolonged benefit. The outcomes of interest for the descriptive analysis are treatment response failure, mortality, hospital admissions, MRSA, CDI, and total antibiotic prescribing.

11 VALIDATION

At a minimum the primary analysis, and safety analysis in the statistical analysis report will be validated. Validation will be conducted by a senior trial statistician or delegate, and will not be the same person who performed the main analysis, or authored the SAP.

12 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

All changes to the protocol or from previous versions of the statistical analysis plan will be detailed in the report.

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14 APPENDICES

APPENDIX I. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) (if applicable)
Primary Objective Effects of PAAP on penicillin prescribing	**Primary Outcome Measures** The proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (Appendix II) up to 12 months post randomisation (SystmOne report/notes review/report, patient follow-up calls)	Up to 12 month post-randomisation Primary Endpoint: Up to 12 months post randomisation
Secondary Objectives 1. To determine whether the PAAP intervention is clinically effective in improving patient health outcomes	**Secondary Outcome Measures** 1. Treatment "response failure" defined as: 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 (SystmOne report), up to 12 months post-randomisation (primary and secondary notes review)	1. Timepoint: Each antibiotic prescription for predefined conditions prompts diary and patient reported outcomes collected for up to 28 days (or until symptoms resolve). Day 28-30 telephone call, will capture the primary outcome data as well. Primary Endpoint: Up to 12 months post-randomisation
2. Effects of PAAP on symptom duration	2. Duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment (diary/research nurse telephone calls)	2. Day 1-28 symptom diary after the first antibiotic prescription identified as a primary event. This will also be collected at day 28-30 by phone call for every antibiotic prescription identified as a primary event

Objectives	Outcome Measures	Timepoint(s) (if applicable)
3. Effects of PAAP on total antibiotic prescribing	3. Total antibiotic use (measured by number of days treatment, number of prescriptions, and Defined Daily Dose (DDD)) and analysed by penicillin/non-penicillin and antibiotic class (SystmOne report/primary care notes review/secondary care notes review/report)	3. Up to 12 months post-randomisation
4. Effects of PAAP on hospital admissions and length of hospital stays	4. Number of hospital admissions and length of hospital stays (Hospital Episode Statistic (primary care notes review/secondary care notes HES-ONS/SystmOne Report)	4. Up to 12 months post-randomisation (continues annually until end of trial)
5. Effects of PAAP on mortality rates	5. Mortality rates between intervention arms (HES/ONS/SystmOne report, primary and secondary care notes review)	5. Up to 12 months post-randomisation
6. Effects of PAAP on Meticillin-resistant *Staphylococcus aureus* (MRSA) infection/colonisation	6. Number of patients with MRSA infection/colonisation (primary and secondary care notes review/SystmOne report)	6. Up to 12 months post-randomisation
7. Effects of PAAP on *Clostridioides difficile* infection	7. Number of patients with *Clostridioides difficile* infection (primary & secondary care notes review, SystmOne report)	7. Up to 12 months post-randomisation
8. To explore patient and clinical views and experiences of penicillin allergy testing, test results, and future antibiotic use	8. GP and patient interviews	8. Qualitative Interviews for GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result
9. (Process evaluation) To explore patient and clinician experiences of trial procedures	9. GP and patient interviews	9. Qualitative Interviews for GPs once their practice has recruited a proportion of patients to the trial and participants once they have received their PAAP result

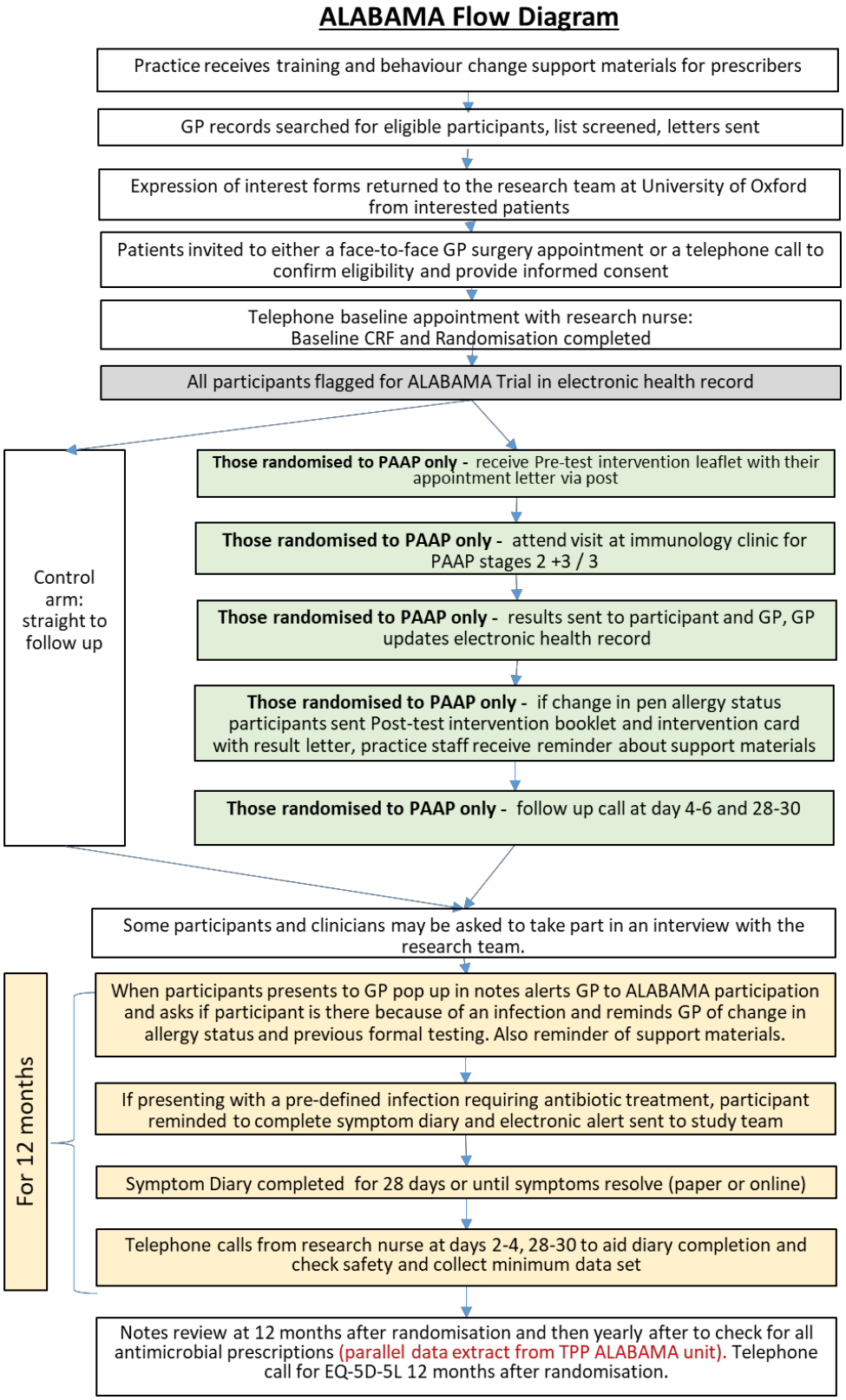
Objectives	Outcome Measures	Timepoint(s) (if applicable)
10. To measure the influences on patient behaviour change regarding consuming penicillin following a negative test result	10. Change in self-reported behaviour and influences on behaviour by patients	10. Participant allergy belief questionnaire (Baseline, D28-30 post-PAAP, D2-4 post-antibiotic episode)
11. Cost effectiveness for the PAAP intervention compared to usual care	11. Self-report health/QoL outcome: EQ-5D-5L will be used a standardised instrument for measuring health outcome at baseline and 1 year. For those that receive antibiotics, EQ-5D-5L will be collected on day 2-4 and day 28-30 after antibiotic treatment. NHS health resource use will be measured through primary and secondary care notes review and linked HES data.	11. EQ-5D-5L will be used as a standardise instrument for measuring health outcome at baseline and 12 months post-randomisation and on day 2-4 and day 28-30 post-antibiotic episode (end point is 12 months post-randomisation). Costs will be measured at 12 months and, through model-based extrapolation, up to 5 years after randomisation
12a. Effect of PAAP on de-labelling at 3 months post-randomisation	12a. The proportion of ALABAMA participants whose labels are removed from the medical eHR record allergy section (primary care notes review)	12a. At 3 months post-randomisation
12b. Effect of PAAP on de-labelling up to 12 months post randomisation	12b. The proportion of ALABAMA participants whose labels were removed and remain removed from the medical eHR record allergy section up to 12 months post-randomisation (primary care notes review)	12b. Up to 12 months post-randomisation
13. Safety outcomes (Exploratory Outcomes)	13. A descriptive analysis will be preformed looking at the safety of de-labelling in the intervention group	13. Up to 12 months post-randomisation
14. Effects of PAAP on all outcomes for follow-up past 12 months	14. Descriptive analysis using data captured in primary and secondary notes review CRF/SystmOne report	14. Until the end of the study

APPENDIX II. COMMON INFECTIONS MANAGED IN THE COMMUNITY FOR WHICH A PENICILLIN IS THE FIRST LINE RECOMMENDED THERAPY

ALABAMA Infections for which an antibiotic prescription would be considered a primary event, and subsequently assessed for primary trial outcome:

- Acute sore throat, pharyngitis, tonsillitis,
- Oral infection,
- Parotitis, salivary gland infection,
- Community acquired pneumonia,
- Chest infections i.e. 'acute bronchitis' or 'lower respiratory infection' or unspecified,
- Acute otitis media,
- Acute bacterial rhinosinusitis,
- Infective COPD exacerbation: amoxicillin or doxycycline first line unless patient at higher risk of treatment failure then co-amoxiclav; empirical treatment or guided by most recent sputum culture and susceptibilities,
- Acute exacerbation of bronchiectasis,
- Skin and soft tissue infection (cellulitis, surgical wound infection, infected ulcer/pressure sore, erysipelas, boil, furuncle, impetigo, etc.),
- Diverticulitis,
- Dental abscesses.

APPENDIX III. TRIAL FLOW DIAGRAM



APPENDIX IV. SCHEDULE OF TRIAL PROCEDURES

	Electronic identification of suitable participants by GP	Eligibility and consent appointment with GP	Baseline appointment by RN (telephone)	Immunology clinical visit for Penicillin allergy test (PAAP)	4-6 days post PAAP RN calls the participant	28-30 days post PAAP RN calls the participant	2 month post-baseline FU – RN calls participant	3 month post-baseline FU – RN calls participant	4 month post-baseline FU – RN calls participant	GP visit + antibiotic episode of trial relevance	2-4 days post antibiotic episode – RN call	28-30 days post antibiotic episode – RN call	12 month post randomisation phone call by RN
							Nested pilot only						
Eligibility	X	X	X										
Consent		X											
Medical history			X										
Penicillin allergy history			X										
Allergy belief questionnaire			X			X					X		
EQ-5D-5L			X								X	X	X
Randomisation			X										
Skin Testing (ST)				X									
Oral Challenge Test (OCT)				X	X								?
Safety: AE/SAE				X	X	X	X	X	X		X	X	
Participant daily diary (28 days)										X	X (Reminder)		
Primary outcome questionnaire												X	
Notes review									X				X

APPENDIX V. DUMMY BASELINE TABLE

	Group A (N=)	Group B (N=)	Overall (N=)
DEMOGRAPHICS & MINIMISATION FACTORS			
Age categories (Randomisation)			
18-64 years, n(%)			
65 years and older, n(%)			
Missing			
Age (years)			
Mean (SD)			
[Range]			
Missing			
Age categories (EudraCT guidelines)			
18-64 years, n(%)			
65-84 years, n(%)			
85 years and older, n(%)			
Missing			
Gender			
Male, n(%)			
Female, n(%)			
Missing			
Ethnicity[1]			
White[2], n(%)			
Mixed or Multiple ethnic groups[3], n(%)			
Asian or Asian British[4], n(%)			
Black, African, Caribbean or Black British[5], n(%)			
Other ethnic group[6], n(%)			
Missing			
Index of Multiple Deprivation Quintile			
1 (Most deprived), n(%)			
2, n(%)			
3, n(%)			
4, n(%)			
5 (Least deprived), n(%)			
Missing			
Number of Antibiotics in the 24 months prior to recruitment (Randomisation)			
Once, n(%)			
Twice, n(%)			
Three times, n(%)			
More than 3 times, n(%)			

	Group A (N=)	Group B (N=)	Overall (N=)
Don't know, n(%)			
Missing			
Number of antibiotic prescriptions in the 24 months prior to recruitment (SystmOne)			
Mean (SD)			
[Range]			
Missing			
Number of QOF registered diseases (Randomisation)			
Mean (SD)			
[Range]			
Missing			
Number of QOF registered diseases (SystmOne)			
Mean (SD)			
[Range]			
Missing			
SYSTMONE MEDICAL HISTORY			
Antibiotic prescriptions in the 12 months prior to recruitment			
Yes, n(%)			
No, n(%)			
Mean (SD)			
[Range]			
Missing			
Antibiotic prescriptions in the 12-24 months prior to recruitment			
Yes, n(%)			
No, n(%)			
Mean (SD)			
[Range]			
Missing			
QOF registered disease[7]			
None, n(%)			
Asthma, n(%)			
Atrial fibrillation, n(%)			
Blood pressure, n(%)			
Cancer, n(%)			
CHD, n(%)			
Chronic kidney disease, n(%)			
COPD, n(%)			
Dementia, n(%)			
Depression, n(%)			
Diabetes, n(%)			

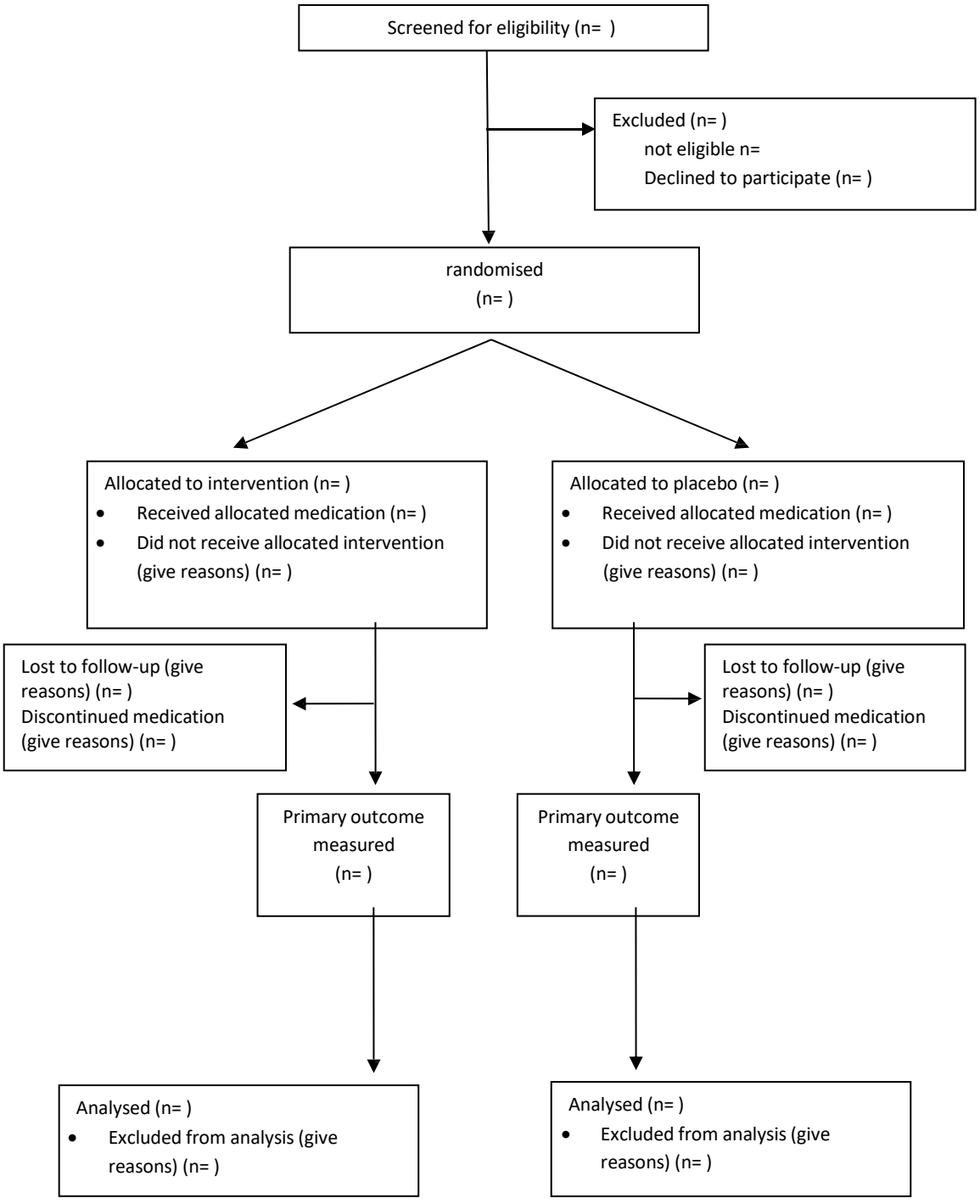
	Group A (N=)	Group B (N=)	Overall (N=)
Epilepsy, n(%)			
Heart failure, n(%)			
Hypertension, n(%)			
Learning disabilities, n(%)			
Mental health, n(%)			
Obesity, n(%)			
Osteoporosis, n(%)			
PAD, n(%)			
Palliative care, n(%)			
Rheumatoid arthritis, n(%)			
Smoking, n(%)			
Stroke, n(%)			
Missing			
PENICILLIN ALLERGY HISTORY (PATIENT REPORTED)			
How long have you been allergic to penicillin?			
<5 years, n(%)			
5-10 years, n(%)			
10-15 years, n(%)			
Over 15 years, n(%)			
Don't know, n(%)			
Missing			
Penicillin that caused the allergic reaction[7]			
Penicillin V, n(%)			
Penicillin G, n(%)			
Ampicillin, n(%)			
Amoxicillin, n(%)			
Co-amoxiclav, n(%)			
Flucloxacillin, n(%)			
Piperacillin/tazobactam, n(%)			
Temocillin, n(%)			
Pivmecillinam, n(%)			
Don't know, n(%)			
Other, n(%)			
Missing			
How was the penicillin that caused the allergic reaction taken			
Oral (by mouth), n(%)			
Injection, n(%)			
Don't know, n(%)			
Missing			
Allergic symptoms[7]			
Red rash (affecting a large part of the body, no blistering, non itchy), n(%)			

	Group A (N=)	Group B (N=)	Overall (N=)
Red rash (affecting a part of the body, no blistering, non itchy), n(%)			
Rash with blistering, n(%)			
Urticaria (red blotchy/itchy rash), n(%)			
Rash (no details known), n(%)			
Swelling of the face, n(%)			
Swelling of the tongue, n(%)			
Swelling of the hands, n(%)			
Swelling of other parts of the body, n(%)			
Difficulty breathing, n(%)			
Sneezing, n(%)			
Nausea, n(%)			
Vomiting, n(%)			
Abdominal discomfort or diarrhoea, n(%)			
Collapse – with loss of consciousness, n(%)			
Don't know/Can't remember, n(%)			
Thrush, n(%)			
Other, n(%)			
Missing			
How long after taking penicillin did you get the allergic reaction?			
After the first dose, n(%)			
During the course (after the second dose) , n(%)			
After the course, n(%)			
Don't know, n(%)			
Missing			
Did you consult with a doctor or attend an emergency department for the allergic reaction?			
Yes, n(%)			
No, n(%)			
Can't remember, n(%)			
Missing			
Were you admitted to hospital?			
Yes, n(%)			
No, n(%)			
Missing			
Do you have an allergic reaction to another group of antibiotics?			
Yes, n(%)			
No, n(%)			

	Group A (N=)	Group B (N=)	Overall (N=)
Missing			
OTHER SIGNIFICANT MEDICAL HISTORY (PATIENT REPORTED)			
Do you have any other medical condition?			
Yes, n(%)			
No, n(%)			
Missing			
Are you pregnant or breast feeding?			
Yes, n(%)			
No, n(%)			
Missing			
Are you currently taking any antihistamines?			
Yes, n(%)			
No, n(%)			
Missing			
Are you currently taking or taken steroids within the last 10 days?			
Yes, n(%)			
No, n(%)			
Missing			
Taking any other medication either prescribed by your GP or bought over the counter?			
Yes, n(%)			
No, n(%)			

NB Percentages have been computed with the number of participants with the response available as the denominator. [1]Collected from medical notes review. [2]Including British, Irish, Gypsy or Irish Traveller, and any other White background. [3]Including White and Black Caribbean, White and Black African, White and Asian, and any other Mixed or Multiple ethnic background. [4]Including Indian, Pakistani, Bangladeshi, Chinese, and other Asian background. [5]Including African, Caribbean, and other Black, African or Caribbean background. [6]Including Arab, and any other ethnic group. [7]Not mutually exclusive.

APPENDIX VI. FLOW DIAGRAM OF TRIAL PARTICIPANTS



NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

UNIVERSITY OF OXFORD

ALABAMA Study
Trial Steering Committee Charter

Trial Full Title:	Penicillin allergy status and its effect on antimicrobial prescribing, patient outcomes, and antimicrobial resistance.
Protocol short title:	ALABAMA: **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resist**A**nce
REC No:	19/LO/0176
ISRCTN Number:	ISRCTN20579216
ClinicalTrials.gov Identifier (if applicable):	
Chief Investigator:	Dr Jonathan Sandoe
Sponsor:	University of Leeds

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1 Introduction

The role of the Trial Steering Committee (TSC) is to provide overall supervision for the ALABAMA trial on behalf of the Trial Sponsor and the Trial Funder and to ensure that the trial is conducted according to the guidelines for Good Clinical Practice (GCP), Research Governance Framework for Health and Social Care and all relevant regulations and local policies.

The background to this trial, its objectives, assessments, interventions, etc., are described in the trial protocol.

The purpose of this document is to define the roles and responsibilities of the trial TSC and to guide its activities, its relationship with other trial committees, its membership, and the format, purpose and timings of its meetings. The charter also describes the procedures for ensuring confidentiality and proper communication to and from the TSC and an outline of the content of the reports to be provided to the TSC.

2 Terms of reference

- To provide advice, through its Chair, to the Trial Management Group (TMG), the Sponsor and the Trial Funder on all aspects of the trial.
- To monitor and supervise the progress of the trial towards its overall objectives, review accrual and results of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the trial and the research question.
- To ensure that the rights, safety and wellbeing of the trial participants are the most important considerations and should prevail over the interests of science and society.
- To ensure that all relevant approvals are obtained before a project begins.
- To agree proposals for substantial protocol amendments and provide advice to the TMG regarding approvals of such amendments.
- To consider the recommendations of Ethics committees, the trial DMEC and/or other trial committees where appropriate.
- The TSC (in conjunction with recommendations from the DMEC where appropriate) should inform the TMG if:
    - There are concerns about the safety of participants
    - Accrual is too low to provide meaningful results
    - It is evident that if the study continues it would fail to provide a clear benefit
- To recommend whether to continue or terminate the study or further adapt it based on safety and efficacy considerations.

3 Membership and Primary responsibilities of the TSC

The ALABAMA TRIAL TSC is a multidisciplinary group comprising of the following members who jointly have responsibility for the design, conduct and evaluation of the clinical research project. Other trial team members can be invited to join meetings as appropriate.

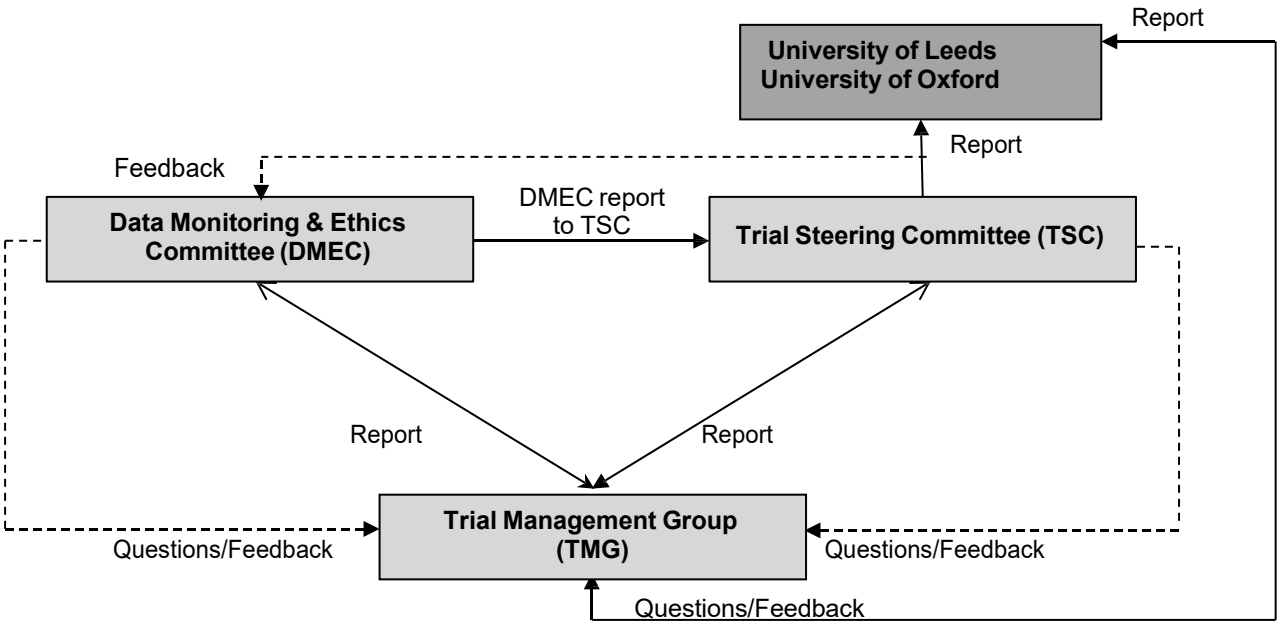
Function	Name	Organisation
Independent Chair	Professor Michael Moore	University of Southampton
Chief Investigator	Dr Jonathan Sandoe	University of Leeds
Co-Chief Investigator	Professor Sue Pavitt	University of Leeds
Co-Investigator	Professor Christopher Butler	University of Oxford
Dependent clinician(s) / statistician(s) or Scientist(s) with relevant experience/ collaborator	Dr Ly-Mee Yu	University of Oxford
Independent clinician(s) or Scientist(s) with relevant experience	Dr Chris Bates	The Phoenix Partnership Not-for-profit organisation
Independent clinician(s) or Scientist(s) with relevant experience	Professor David Ford	University of Swansea: Centre for Improvement in Population Health through E-records Research (CIPHER)
Independent clinician(s) or Scientist(s) with relevant experience	Dr Alice Oborne	St Thomas Hospital, London
Independent clinician(s) or Scientist(s) with relevant experience	Dr Achyut Guleri	Blackpool Teaching Hospitals NHS Foundation Trust / University of Central Lancashire
Independent clinician(s) or Scientist(s) with relevant experience	Dr Shuayb Elkhalifa	University of Manchester
Independent clinician(s) or Scientist(s) with relevant experience	Dr Hazel Everitt	University of Southampton
Representative of relevant patient group	Jenny Boards	Leeds Teaching Hospital NHS FT

Representatives of the Sponsor (PC-CTU) and other members of the research team will be invited to attend TSC meeting as appropriate.

The responsibility for calling and organising TSC meetings lies with the Chief Investigator (CI) in association with the Chair. The Chair assisted by the CI is responsible for facilitating the meetings and summarising discussions.

The TSC membership is for the duration of the trial. If any members leave the TSC, the TMG should provide replacements promptly for appointment by the Chair.
Independent committee members will be reimbursed for reasonable travel expenses for attending meetings. The lay representative will be reimbursed for reasonable travel expenses and may receive an honorarium of £70 per TSC meeting attended. No other payments will be made to the professional members.

Possible Interactions between TSC and other study committees



4 Agreements

TSC members should formally register their agreement to be a member of the committee as well as their agreement with the contents of the charter, trial confidentiality and should declare any potential conflicts of interest.

Independent members should complete and return a signed agreement and competing interests form provided at the end of this charter.

5 Responsibilities

The TSC will provide overall supervision of the conduct of the trial on behalf of the Trial Sponsor and Trial Funder and will ensure that the trial is conducted to the rigorous standards set out in the Department of

Health's Research Governance Framework for Health and Social Care and according to the principles of the Guidelines for Good Clinical Practice. Responsibilities of the TSC to include:

- Reviewing selection/recruitment/retention of participants and their management.
- Finalising and reviewing study protocol, and other selected study documentation if appropriate.
- Determine if amendments to the protocol or changes to study conduct are required and deciding on changes to these and to study conduct in general. Any changes to essential trial documentation or conduct must be notified to the TSC.
- Reviewing adherence to the protocol by investigators and participants.
- Assessing integrity and completeness of data collected, guided by the DMEC.
- Monitoring the overall conduct of the trial, ensuring that it follows the standards set out in the guidelines of GCP, assessing the safety and efficacy of the interventions, recruitment figures and completion of trial assessments in association with the DMEC report.
- Reviewing, commenting and considering whether to request an extension (together with the funder).
- Reviewing the recommendations of the DMEC (if applicable) and/or other study committees and suggesting appropriate action to the TMG.
- Endorsing the statistical analysis plan which is approved by DMEC.
- Considering the ethical implications of any recommendation made by DMEC.
- Monitoring the progress of trial and deciding on appropriate action in order to maximise the chances of completing it within the agreed timelines.
- Monitor continuing appropriateness of patient information.
- Considering new information relevant to the study e.g. results from other studies that may have a bearing to the conduct of the study and deciding on appropriate action.

The TSC may recommend early termination of the trial or modification of the study design in the event of a clear outcome derived from accumulating data or on the basis of information available from other sources or on safety grounds. This includes but is not limited to the following reasons:

a. Animal, human or toxicological test results, which in the reasonable determination of the TSC, support termination of the trial
b. Ethical or patient safety issues occur that the TSC feels support termination of the trial
c. Extraordinary scientific, regulatory or other events that negatively impact the rationale for the trial, such that the TSC agrees it is appropriate to terminate the trial

The TSC should be available to provide independent advice as required not just when meetings are scheduled.

The TSC should maintain confidentiality of all information it receives.
Members should not discuss confidential issues from their involvement in the study until the primary results have been published.

6 Role of the TSC Chair

- Arrange the first meeting of the TSC with the assistance of the CI to agree contents of charter and set up schedule of meetings.

- Establish clear reporting lines – to the Funder and Sponsor.
- Become familiar with the role of the DMEC.
- Provide an independent, experienced opinion if conflicts arise between the needs of the research team, the Funder, the Sponsor and/or any other agencies.
- Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems.
- Ensuring that substantial changes to the protocol are endorsed by other members of the TSC.

7 TSC meetings

- The responsibility for calling and organising a TSC meeting lies with the CI in association with the TSC Chair.
- The TMG will organise these on behalf of the CI.
- TSC meetings can be in person but also by teleconference, based on availability of TSC members.
- All TSC members will be provided with relevant study documents and the TSC report one week prior to the meeting.
- The first TSC meeting should ideally be held face-to-face to discuss, revise and finalise the terms of reference, agree the content of the TSC charter and sign any declaration, and agree the frequency of the meetings.
- Frequency of subsequent meetings will be six monthly. Dependent on the number of issues that need the TSC's attention, this frequency could be increased or decreased (e.g., when interim analysis has been completed).
- Meetings can also be held at any time at the request of the CI or TSC chair.
- The final TSC meeting will be arranged when target recruitment is completed, all data collected and cleaned and the database is locked. This final meeting will be held to discuss final/completed data and interpretation, and publication timelines. If the study is terminated prematurely, no final study meeting is required.

8 Attendance

Every effort will be made to ensure that all TSC members can attend the meetings. The Trial Manager should try to find a date that enables this. The CI must try to attend all meetings, especially if major actions are expected.

More than half of the committee members should be attending (either in person or via teleconference) the TSC for any decisions to be valid. This must include the CI and at least two independent members (including the chair).

If the TSC is considering major actions the TSC Chair should communicate with absent members, including the CI, as soon after the meeting as possible to determine whether they all agree. If there is disagreement amongst absent members a further meeting should be arranged with the full TSC.

9 Reporting

Prior to a TSC meeting a report will be prepared by the TMG with input from Trial Manager, Data Manager, Statistician and circulated to TSC members at least a week (or as otherwise agreed) before the meeting.

On consideration of the information presented at these meetings, the TSC should provide recommendations of appropriate action in writing to the TMG who will be responsible for implementing any actions. The TSC may also provide feedback to the DMEC and where appropriate to the Sponsor/Funder.

Minutes of the meeting including key points and actions will be prepared by the Trial Manager. These minutes will describe the proceedings and include the recommendations of the TSC. All members of the TSC must agree the minutes and these will be signed off by the TSC Chair on behalf of all members. Minutes will be circulated to all TSC members, the TMG, and, if appropriate, the Sponsor and the Trial Funder. Approved Minutes will be filed in the Trial Master File.

Decisions and recommendations by the TSC should be unanimous. If not a vote may be taken. The role of the Chair is to summarise discussions and encourage consensus. Therefore it is best for the chair to give his own opinion last. It is important that the implications (ethical, statistical, practical and financial) for the trial be considered before any decision is made.

10 Contents of the TSC Reports

An outline of the contents of the TSC report is given below:

- Outline of the study design, sample size sought and current available evidence
- Statistical consideration and design before database lock
- Major protocol amendments
- Patient screening
- Eligibility violations
- Protocol violations by investigators or participants
- Study accrual by month/total (by site and overall)
- Completeness and quality of data collected/CRF return, especially ‘how many are seen’, and ‘loss to follow-up’
- CRF return, entry into database
- Baseline characteristics for the whole population
- Safety reporting (SAEs, SUSARS etc.)
- Follow-up data available
- Any matters affecting the trial
- Compliance by patients to clinic visit and adherence to medication
- Latest ‘open’ DMEC report and DMEC recommendations

11 Conflicts of interest

TSC members should not have any apparent financial, scientific or intellectual conflict of interest that could prevent them from objectively reviewing the study protocol, interim and final data and giving advice to the TMG. TSC members should disclose to the Chair any other conflicts they consider relevant. Any

members who develop significant conflicts of interest during the course of the trial should resign from the TSC.

12 Publication

TSC members will be asked to approve the confidential draft manuscript describing the primary results prior to submission for publication and they will be acknowledged in reports relating to the primary outcomes of the trial. The CI will be the corresponding author on publications relating to the primary outcomes of the trial.

13 Annexe 1

Agreement and competing interests form for independent members of the ALABAMA Trial Steering Committee.

Please complete the following document and post a hard copy of the whole document to:
Mina Davoudianfar, Nuffield Department of Primary Care Health Sciences, University of Oxford, Gibson Building, Radcliffe Observatory, Oxford, OX2 6GG

Alternatively scan and email it to alabama@phc.ox.ac.uk

☐ I have read and understood the TSC charter v1.0 dated 15 Feb 2019

☐ I agree to join the TSC for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidential

The avoidance of any perception that members of the TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.
Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) TSC member should remove the conflict or stop participating in the TSC. Table 1 lists potential competing interests:

Table 1: Potential competing interests for independent members

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1. Stock ownership in any commercial companies involved.
2. Stock transaction in any commercial company involved (if previously holding stock)
3. Consulting arrangements with the Sponsor
4. Frequent speaking engagements on behalf of the intervention
5. Career tied up in a product or technique assessed by the trial
6. Hands-on participation in the trial
7. Involvement in the running of the trial
8. Emotional involvement in the trial
9. Intellectual conflict e.g. strong prior belief in the trial's experimental arm
10. Involvement in regulatory issues relevant to the trial procedures
11. Investment (financial or intellectual) in competing products
12. Involvement in the publication
13. Other:

☐ **NO,** I have no competing interests to declare

☐ **YES,** I have competing interests to declare (please detail below)

_____

_____

Name: _____

Signed: _____ Date: _____

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
Primary Care Clinical Trials Unit

ALABAMA Study
Data Monitoring Committee Charter

Trial Full Title:	Penicillin allergy status and its effect on antimicrobial prescribing, patient outcomes, and antimicrobial resistance
Protocol short title:	ALABAMA: ALlergy AntiBiotics And Microbial resistAnce
REC No:	19/LO/0176
ISRCTN Number:	ISRCTN20579216
ClinicalTrials.gov Identifier (if applicable):	
Chief Investigator:	Dr Jonathan Sandoe
Sponsor:	University of Leeds
Sponsors Reference:	NA

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1 INTRODUCTION

The role of the Data Monitoring Committee (DMC) is to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, to ensure continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the clinical trial. The DMC is independent from the trial team.

The purpose of this document is to describe the roles and responsibilities of the independent DMC for the ALABAMA trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.

The background to this trial, its objectives, assessments, interventions, etc., are described in the trial protocol.

2 ROLES AND RESPONSIBILITIES

The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

The DMC should inform the Chair of the TSC if, in their view:

(i) The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; **or**

(ii) It becomes evident that no clear outcome is likely to be obtained.

The specific role of the DMC includes the interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. The DMC will also review the data after the first 96 participants have been recruited and four months follow up completed (as part of the nested pilot).

The DMC may also fulfil the following roles, as appropriate for the stage of the trial and/or in response to other information made available to the DMC:

- Assess data quality, including completeness (and by so doing encourage collection of high quality data).
- Monitor recruitment figures and losses to follow-up.
- Monitor compliance with the protocol by participants and investigators.
- Monitor trial conduct – organisation and implementation of trial protocol (the DMC should only perform this role in the absence of other trial oversight committees).
- Monitoring evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths).
- Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.
- Suggest additional data analyses.

- Advise on protocol modifications suggested by investigators or Sponsor (e.g. to inclusion criteria, trial endpoints, or sample size).
- Monitor planned sample size assumptions.
- Review and approve the statistical analysis plan.
- Monitor continuing appropriateness of patient information.
- Monitor compliance with previous DMC recommendations.
- Assess the impact and relevance of external evidence.

3 MEMBERSHIP OF THE COMMITTEE

The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial coordinating centre (Annex 1).

If any potential conflicts of interest arise during the conduct of the trial the DMC member should notify the DMC chair and the Chair of the TSC. If the DMC chair develops a potential conflict they should notify the Chair of the TSC.

The members of the DMC for this trial are:

Function	**Name**	**Organization**
Independent Chair (Independent Statistician)	Dr Beth Stuart	University of Southampton
Independent clinician(s) or Scientist(s) with relevant experience (Allergy and Immunology)	Dr Ravishankar Sargur	Sheffield Teaching Hospitals NHS Foundation Trust
Independent clinician(s) or Scientist(s) with relevant experience (Pharmacist)	Dr David Gerrett	NHS England

The DMC membership will include a statistician to provide independent statistical expertise.

The trial statistician, will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.

The trial office team (e.g. Trial Manager, etc.) usually only inputs to the production of the non-confidential sections of the DMC report. The CI, may be asked, and should be available, to attend open sessions of the DMC meeting, and his absence should be specifically agreed with the DMC Chair. The other Trial Management Group members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).

4 ORGANISATION OF DMC MEETINGS

The DMC will meet at least once a year, but will also review all planned interim analyses. The first meeting should, where feasible, be face-to-face to facilitate full discussion and allow members to get to know each other, but future meetings can be held via teleconference if necessary.

The meetings will consist of:

1. Open session: Introduction and review and discussion of the "open" parts of the report
2. Closed session: DMC discussion of "closed" parts of the report

Every effort will be made to ensure that all DMC members can attend the meetings. The Trial Manager should try to find a date that enables this. The CI must try to attend all meetings, especially if major actions are expected. All three members of the committee should be attending the DMC (either in person or via teleconference) for any decisions to be valid. This must include the CI and the other three independent members (including the chair). will be given access of accumulating data and unblinded interim analysis results. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the CI.

5 DECISION MAKING

Possible recommendations by the DMC could include:

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
- Stopping recruitment within a subgroup
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
- Stopping a single arm of a multi-arm trial
- Sanctioning and/or proposing protocol changes

The ALABAMA trial includes a nested-pilot to the main trial and stop/go criteria must be reviewed by the DMC before recruitment into the main trial can continue. The stop/go criteria are:

- Recruitment – has the target been achieved or appropriate process modifications implemented so rate is adequate?
- Early adverse event rate after PAAP exposure – compared to the anticipated rate. This will not be quantified for the stop / go criteria but will be assessed qualitatively.

The DMC will inform the TSC of any recommendations based on the review of the stop/go criteria.

It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made.

Effort should be made for all members to attend. The trials office team will try to ensure that a date is chosen to enable this. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet

if at least one statistician and one clinician, including the Chair (unless otherwise agreed), will be present. If the DMC is considering recommending major action after such a meeting the DMC Chair should talk with the absent members as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full DMC.

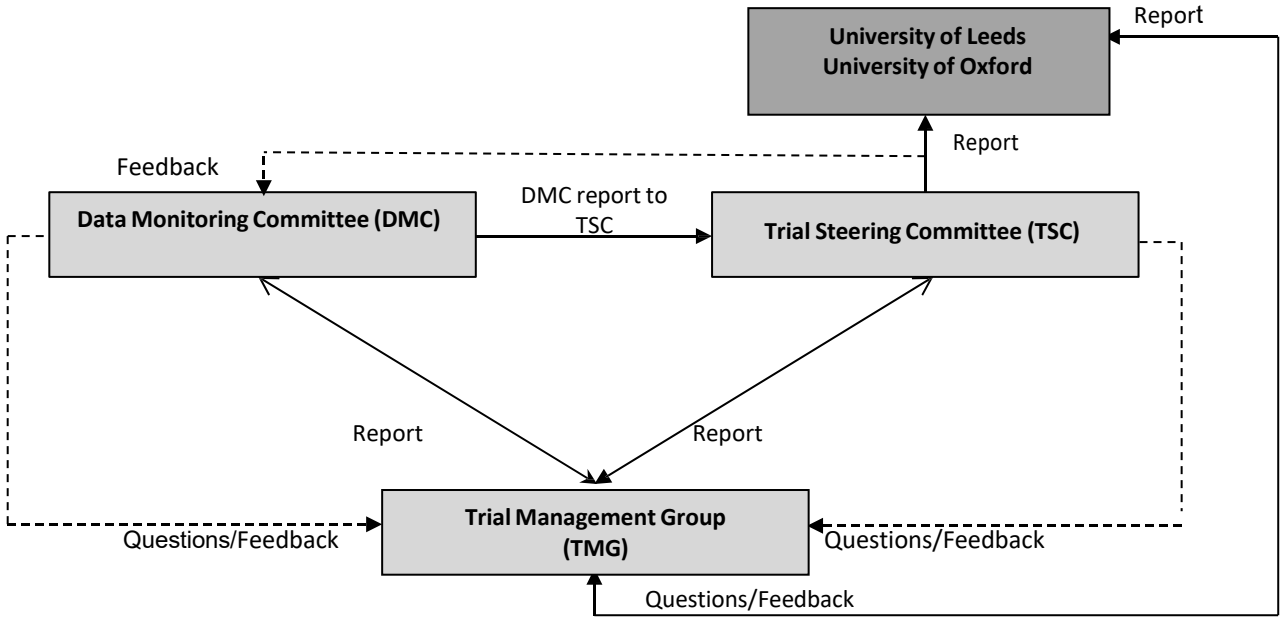
6 REPORTING

The DMC chair should communicate to the TSC Chair via letter within 2 weeks of the DMC meeting. It is customary that the DMC does not make decisions about the trial, but rather makes recommendations to an appropriate executive committee or its Chair.

Open session minutes will be kept by the trial manager and stored at Primary Care Clinical Trials Unit, University of Oxford. Closed session minutes will be taken by a DMC member appointed by the DMC chair and stored with the DMC Chair until the conclusion of the trial at which time they should provide all closed session minutes to the TSC.

If the DMC has serious problems or concerns with the TSC decision a meeting of these groups should be held. The information to be shown would depend upon the action proposed and the DMC's concerns. Depending on the reason for the disagreement confidential data will often have to be revealed to all those attending such a meeting. The meeting should be chaired by a senior member of the PC-CTU staff or an external expert who is not directly involved with the trial.

8.1 Interaction between DMC and other study committees



7 AFTER THE TRIAL

At the end of the trial there may be a meeting to allow the DMC to discuss the final data with principal trial investigators/Sponsors and give advice about data interpretation. The trial results will be published in a correct and timely manner.

DMC members should be named and their affiliations listed in the main report, unless they explicitly request otherwise. A brief summary of the timings and conclusions of DMC meetings should be included in the body of this paper.

The DMC may wish to be given the opportunity to read and comment on any publications before submission. DMC should treat trial results as confidential until after trial results have been published, or when permission is agreed with the Trial Management Group.

8 PAYMENTS

Members will not receive payment for being a member of the DMC, but will be reimbursed for travel and accommodation.

9 Annex 1: Agreement and competing interests form for the independent members of the ALABAMA DMC

Please complete the following document and return the whole document to: Mina Davoudianfar
Preferably scanned and emailed to Alabama@phc.ox.ac.uk , alternatively post a hardcopy to:

Mina Davoudianfar, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Primary Care Building, Radcliffe Observatory, Oxford, OX2 6GG.

☐ I have read and understood the DMC charter version 1 15 Feb 2019

☐ I agree to join the DMC for this trial as an independent member

☐ I agree to treat all sensitive trial data and discussions confidential

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC.

Potential Competing Interests:

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
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- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products
- Involvement in the publication
- Other

☐ **No,** I have no competing interests to declare

☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

Name: _____ Signed: _____ Date: _____

10 Annex 2: Suggested repot from DMC to TSC where no Recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear *[Chair of Trial Steering Committee]*

The Data Monitoring Committee (DMC) for the *[insert trial name]* trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

*[*Name of meeting Chair*]*
Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]

(3) [*Insert name and role*]

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES
Primary Care Clinical Trials Unit

ALABAMA Study
Data Monitoring Committee Charter

Trial Full Title:	Penicillin allergy status and its effect on antimicrobial prescribing, patient outcomes, and antimicrobial resistance
Protocol short title:	ALABAMA: ALlergy AntiBiotics And Microbial resistAnce
REC No:	19/LO/0176
ISRCTN Number:	ISRCTN20579216
ClinicalTrials.gov Identifier (if applicable):	
Chief Investigator:	Dr Jonathan Sandoe
Sponsor:	University of Leeds
Sponsors Reference:	NA

Table of Contents

1 INTRODUCTION

The role of the Data Monitoring Committee (DMC) is to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, to ensure continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the clinical trial. The DMC is independent from the trial team.

The purpose of this document is to describe the roles and responsibilities of the independent DMC for the ALABAMA trial, including the timing of meetings, methods of providing information to and from the DMC, frequency and format of meetings, statistical issues and relationships with other committees.

The background to this trial, its objectives, assessments, interventions, etc., are described in the trial protocol.

2 ROLES AND RESPONSIBILITIES

The DMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the Trial Steering Committee (TSC).

The DMC should inform the Chair of the TSC if, in their view:

(i) The results are likely to convince a broad range of clinicians, including those supporting the trial and the general clinical community, that one trial arm is clearly indicated or contraindicated, and there was a reasonable expectation that this new evidence would materially influence patient management; **or**

(ii) It becomes evident that no clear outcome is likely to be obtained.

The specific role of the DMC includes the interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. The DMC will also review the data after the first 96 participants have been recruited and four months follow up completed (as part of the nested pilot).

The DMC may also fulfil the following roles, as appropriate for the stage of the trial and/or in response to other information made available to the DMC:

- Assess data quality, including completeness (and by so doing encourage collection of high quality data).
- Monitor recruitment figures and losses to follow-up.
- Monitor compliance with the protocol by participants and investigators.
- Monitor trial conduct – organisation and implementation of trial protocol (the DMC should only perform this role in the absence of other trial oversight committees).
- Monitoring evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for treatment harm (e.g. toxicity data, SAEs, deaths).
- Decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups.
- Suggest additional data analyses.

- Advise on protocol modifications suggested by investigators or Sponsor (e.g. to inclusion criteria, trial endpoints, or sample size).
- Monitor planned sample size assumptions.
- Review and approve the statistical analysis plan.
- Monitor continuing appropriateness of patient information.
- Monitor compliance with previous DMC recommendations.
- Assess the impact and relevance of external evidence.

3 MEMBERSHIP OF THE COMMITTEE

The members should be independent of the trial (e.g. should not be involved with the trial in any other way or have some competing interest that could impact on the trial). Any competing interests, both real and potential, should be declared. A short competing interest form should be completed and returned by the DMC members to the trial coordinating centre (Annex 1).

If any potential conflicts of interest arise during the conduct of the trial the DMC member should notify the DMC chair and the Chair of the TSC. If the DMC chair develops a potential conflict they should notify the Chair of the TSC.

The members of the DMC for this trial are:

Function	**Name**	**Organization**
Independent Chair (Independent Statistician)	Dr Beth Stuart	University of Southampton
Independent clinician(s) or Scientist(s) with relevant experience (Allergy and Immunology)	Prof Thirumala Krishna	University Hospital Birmingham NHS Foundation Trust
Independent clinician(s) or Scientist(s) with relevant experience (Pharmacist)	Tony Jamieson	NHS England

The DMC membership will include a statistician to provide independent statistical expertise.

The trial statistician, will produce (or oversee the production of) the report to the DMC and will participate in DMC meetings, guiding the DMC through the report, participating in DMC discussions and, on some occasions, taking notes.

The trial office team (e.g. Trial Manager, etc.) usually only inputs to the production of the non-confidential sections of the DMC report. The CI, may be asked, and should be available, to attend open sessions of the DMC meeting, and his absence should be specifically agreed with the DMC Chair. The other Trial Management Group members will not usually be expected to attend but can attend open sessions when necessary (See Organisation of DMC Meetings).

4 ORGANISATION OF DMC MEETINGS

The DMC will meet at least once a year, but will also review all planned interim analyses. The first meeting should, where feasible, be face-to-face to facilitate full discussion and allow members to get to know each other, but future meetings can be held via teleconference if necessary.

The meetings will consist of:

1. Open session: Introduction and review and discussion of the "open" parts of the report
2. Closed session: DMC discussion of "closed" parts of the report

Every effort will be made to ensure that all DMC members can attend the meetings. The Trial Manager should try to find a date that enables this. The CI must try to attend all meetings, especially if major actions are expected. All three members of the committee should be attending the DMC (either in person or via teleconference) for any decisions to be valid. This must include the CI and the other three independent members (including the chair). will be given access of accumulating data and unblinded interim analysis results. DMC members do **not** have the right to share confidential information with anyone outside the DMC, including the CI.

5 DECISION MAKING

Possible recommendations by the DMC could include:

- No action needed, trial continues as planned
- Early stopping due, for example, to clear benefit or harm of a treatment, futility, or external evidence
- Stopping recruitment within a subgroup
- Extending recruitment (based on actual control arm response rates being different to predicted rather than on emerging differences) or extending follow-up
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It is recommended that every effort should be made for the DMC to reach a unanimous decision. If the DMC cannot achieve this, a vote may be taken, although details of the vote should not be routinely included in the report to the TSC as these may inappropriately convey information about the state of the trial data. It is important that the implications (e.g. ethical, statistical, practical, and financial) for the trial be considered before any recommendation is made.

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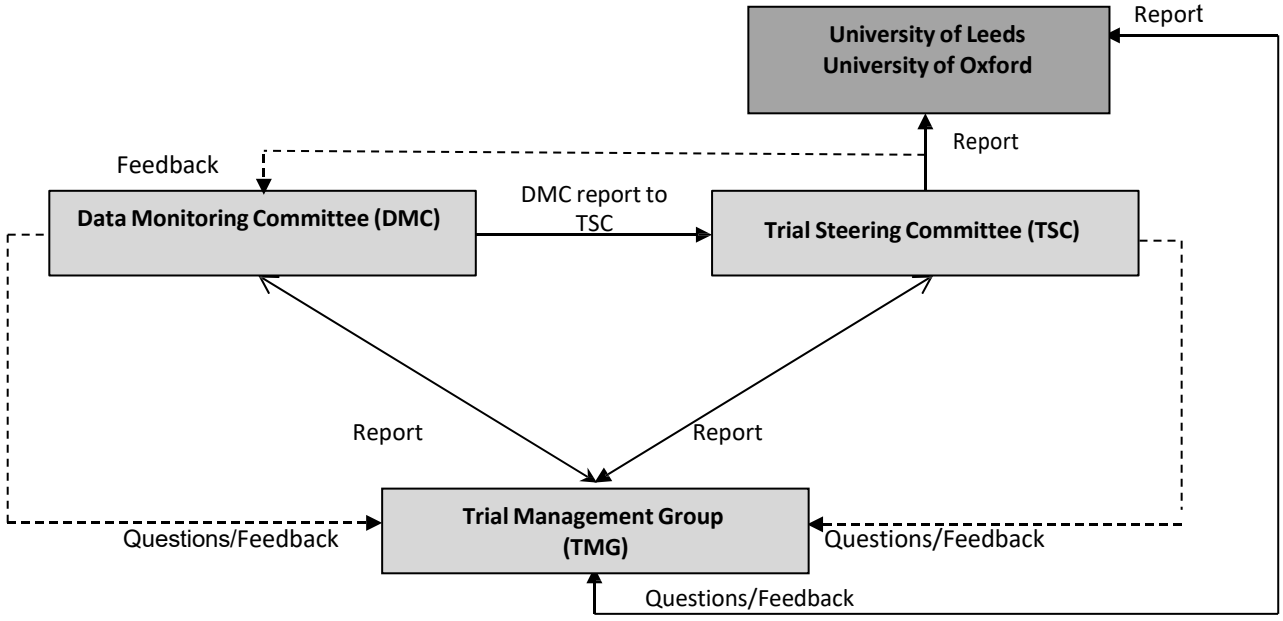

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8 PAYMENTS

Members will not receive payment for being a member of the DMC, but will be reimbursed for travel and accommodation.

9 Annex 1: Agreement and competing interests form for the independent members of the ALABAMA DMC

Please complete the following document and return the whole document to: Kelsey Armitage
Preferably emailed to Alabama@phc.ox.ac.uk , alternatively post a hardcopy to:

Kelsey Armitage , Nuffield Department of Primary Care Health Sciences, University of Oxford, Gibson Building, Radcliffe Observatory, Oxford, OX2 6GG.

☐ I have read and understood the DMC charter version 2 11 Feb 2022

☐ I agree to join the DMC for this trial as an independent member

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The avoidance of any perception that members of a DMC may be biased in some fashion is important for the credibility of the decisions made by the DMC and for the integrity of the trial.

Possible competing interest should be disclosed via the trials office. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC.

Potential Competing Interests:

- Stock ownership in any commercial companies involved
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- Investment (financial or intellectual) in competing products
- Involvement in the publication
- Other

☐ **No,** I have no competing interests to declare

☐ **Yes,** I have competing interests to declare (please detail below)

Please provide details of any competing interests: _____

_____

_____

Name: _____ Signed: _____ Date: _____

10 Annex 2: Suggested repot from DMC to TSC where no Recommendations are being made

[Insert date]

To: Chair of Trial Steering Committee

Dear *[Chair of Trial Steering Committee]*

The Data Monitoring Committee (DMC) for the *[insert trial name]* trial met on *[meeting date]* to review its progress and interim accumulating data. *[List members] attended* the meeting and reviewed the report.

We congratulate the trial organisers and collaborators on the progress and conduct of the trial and the presentation of the data. The trial question remains important and, on the basis of the data reviewed at this stage, we recommend continuation of the trial according to the current version of the protocol *[specify protocol version number and date]* with no changes.

We shall next review the progress and data *[provide approximate timing]*

Yours sincerely,

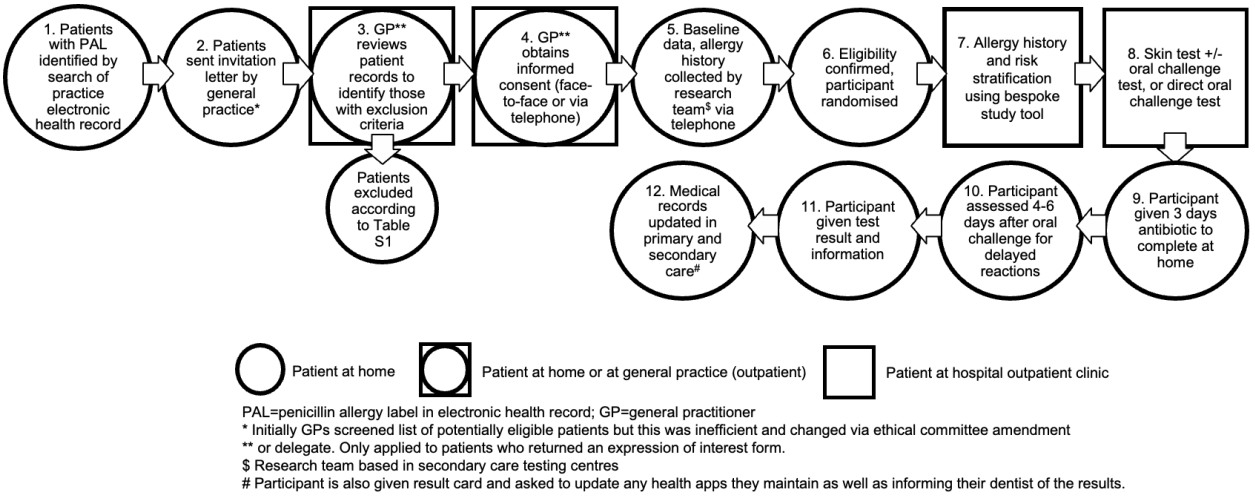
*[*Name of meeting Chair*]*
Chair of Data Monitoring Committee

On behalf of the DMC (all members listed below)

DMC members:
(1) [*Insert name and role*]
(2) [*Insert name and role*]

(3) [*Insert name and role*]

Figure S1 Trial recruitment processes, participant journey and location during each stage of of the ALABAMA penicillin allergy assessment RCT



PAL=penicillin allergy label in electronic health record; GP=general practitioner
* Initially GPs screened list of potentially eligible patients but this was inefficient and changed via ethical committee amendment
** or delegate. Only applied to patients who returned an expression of interest form.
$ Research team based in secondary care testing centres
# Participant is also given result card and asked to update any health apps they maintain as well as informing their dentist of the results.

Table S1 Infections for which an antibiotic prescription was a primary event

Acute bacterial rhinosinusitis
Acute exacerbation of bronchiectasis
Acute otitis media
Acute sore throat, pharyngitis, tonsillitis
Chest infections i.e. 'acute bronchitis' or ’lower respiratory infection’ or unspecified
Community acquired pneumonia
Dental abscesses
Diverticulitis
Infective COPD exacerbation: amoxicillin or doxycycline first line unless patient at higher risk of treatment failure then co-amoxiclav; empirical treatment or guided by most recent sputum culture and susceptibilities
Oral infection
Parotitis, salivary gland infection
Skin and soft tissue infection (cellulitis, surgical wound infection, infected ulcer/pressure sore, erysipelas, boil, faruncule, impetigo etc)

Table S2 Patient reported medical history at baseline assessment

	Penicillin allergy test (N=401)	Usual clinical care (N=410)	Overall (N=811)
Duration of allergic to penicillin, n (%)			
<5 years	21 (5·2%)	21 (5·1%)	42 (5·2%)
5-10 years	18 (4·5%)	29 (7·1%)	47 (5·8%)
10-15 years	30 (7·5%)	24 (5·9%)	54 (6·7%)
Over 15 years	319 (79·6%)	329 (80·2%)	648 (79·9%)
Don't know	13 (3·2%)	7 (1·7%)	20 (2·5%)
Penicillin that caused the allergic reaction*, n (%)			
Penicillin V	8 (2·0%)	17 (4·1%)	25 (3·1%)
Penicillin G	2 (0·5%)	0 (0·0%)	2 (0·2%)
Ampicillin	4 (1·0%)	6 (1·5%)	10 (1·2%)
Amoxicillin	68 (17·0%)	52 (12·7%)	120 (14·8%)
Co-amoxiclav	6 (1·5%)	12 (2·9%)	18 (2·2%)
Flucloxacillin	12 (3·0%)	13 (3·2%)	25 (3·1%)
Piperacillin/tazobactam	0 (0·0%)	0 (0·0%)	0 (0·0%)
Temocillin	0 (0·0%)	0 (0·0%)	0 (0·0%)
Pivmecillinam	0 (0·0%)	1 (0·2%)	1 (0·1%)
Don't know	303 (75·6%)	310 (75·6%)	613 (75·6%)
Penicillin that caused the allergic reaction taken*, n(%)			
Oral (by mouth)	308 (76·8%)	298 (72·7%)	606 (74·7%)
Injection	11 (2·7%)	13 (3·2%)	24 (3·0%)
Don't know	84 (20·9%)	97 (23·7%)	181 (22·3%)
Missing	*0*	*2*	*2*
Allergic symptoms*, n(%)			
Red rash (affecting a large part of the body, no blistering, non itchy)	27 (6·7%)	29 (7·1%)	56 (6·9%)
Red rash (affecting a part of the body, no blistering, non itchy)	18 (4·5%)	30 (7·3%)	48 (5·9%)
Rash with blistering	4 (1·0%)	7 (1·7%)	11 (1·4%)
Urticaria (red blotchy/itchy rash)	124 (30·9%)	107 (26·1%)	231 (28·5%)
Rash (no details known)	89 (22·2%)	94 (22·9%)	183 (22·6%)
Swelling of the face	19 (4·7%)	11 (2·7%)	30 (3·7%)
Swelling of the tongue	2 (0·5%)	2 (0·5%)	4 (0·5%)
Swelling of the hands	4 (1·0%)	2 (0·5%)	6 (0·7%)
Swelling of other parts of the body	11 (2·7%)	17 (4·1%)	28 (3·5%)
Difficulty breathing	5 (1·2%)	4 (1·0%)	9 (1·1%)
Sneezing	0 (0·0%)	0 (0·0%)	0 (0·0%)
Nausea	18 (4·5%)	18 (4·4%)	36 (4·4%)

	Penicillin allergy test (N=401)	Usual clinical care (N=410)	Overall (N=811)
Vomiting	35 (8·7%)	31 (7·6%)	66 (8·1%)
Abdominal discomfort or diarrhoea	23 (5·7%)	29 (7·1%)	52 (6·4%)
Collapse – with loss of consciousness	0 (0·0%)	2 (0·5%)	2 (0·2%)
Thrush	2 (0·5%)	3 (0·7%)	5 (0·6%)
Don't know/Can't remember	77 (19·2%)	88 (21·5%)	165 (20·3%)
Other	73 (18·2%)	78 (19·0%)	151 (18·6%)
Duration after taking penicillin that gave the allergic reaction, n(%)			
After the first dose	49 (12·2%)	54 (13·3%)	103 (12·8%)
During the course (after the second dose)	144 (35·9%)	139 (34·2%)	283 (35·1%)
After the course	13 (3·2%)	5 (1·2%)	18 (2·2%)
Don't know	195 (48·6%)	208 (51·2%)	403 (49·9%)
Missing	*0*	*4*	*4*
Consulted with a doctor or attend an emergency department for the allergic reaction, n(%)			
Yes	300 (74·8%)	302 (73·8%)	602 (74·3%)
No	37 (9·2%)	31 (7·6%)	68 (8·4%)
Can't remember	64 (16·0%)	76 (18·6%)	140 (17·3%)
Missing	*0*	*1*	*1*
Had admitted to hospital due to the allergic reaction, n(%)			
Yes	10 (2·5%)	6 (1·5%)	16 (2·0%)
No	348 (86·8%)	339 (82·9%)	687 (84·8%)
Can't remember	43 (10·7%)	64 (15·6%)	107 (13·2%)
Missing	*0*	*1*	*1*
An allergic reaction to another group of antibiotics, n(%)	89 (22·2%)	96 (23·4%)	185 (22·8%)
Have any other medical condition, n(%)	283 (70·6%)	299 (72·9%)	582 (71·8%)
Currently pregnant or breast feeding, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Currently taking any antihistamines, n(%)	51 (12·7%)	49 (12·0%)	100 (12·3%)
Currently taking or taken steroids within the last 10 days, n(%)	3 (0·7%)	2 (0·5%)	5 (0·6%)
Taking any other medication either prescribed by your GP or bought over the counter, n(%)	302 (75·3%)	321 (78·3%)	623 (76·8%)

NB Percentages have been computed using the number of participants with any given response available as the denominator.
*Not mutually exclusive.

Table S3 Participant minimisation factors at baseline assessment in the ALABAMA trial

	Penicillin allergy test (N=401)	Usual clinical care (N=410)	Overall (N=811)
Age categories, n(%)			
18-64 years	272 (67·8%)	282 (68·8%)	554 (68·3%)
65 years and older	129 (32·2%)	128 (31·2%)	257 (31·7%)
Number of antibiotics in the 24 months prior to recruitment, n(%)			
One	262 (65·3%)	268 (65·4%)	530 (65·4%)
Two	66 (16·5%)	66 (16·1%)	132 (16·3%)
Three	31 (7·7%)	33 (8·0%)	64 (7·9%)
More than three	42 (10·5%)	43 (10·5%)	85 (10·5%)
Number of comorbidities*, n(%)			
None	77 (19·2%)	79 (19·3%)	156 (19·2%)
One – two	215 (53·6%)	220 (53·7%)	435 (53·6%)
Three or more	109 (27·2%)	111 (27·1%)	220 (27·1%)

*Comorbidities were quality outcome framework registered diseases.

Table S4 Availability of outcome data at each assessment timepoint

	Penicillin allergy test (N=401)	Usual clinical care (N=410)	Overall (N=811)
Primary outcome, n(%)	401 (100·0%)	410 (100·0%)	811 (100·0%)
Treatment "response failure", n(%)	401 (100·0%)	410 (100·0%)	811 (100·0%)
Duration of symptoms rated 'moderately bad' or worse, n(%)	113 (28·2%)	116 (28·3%)	229 (28·2%)
Antibiotic usage, n(%)	401 (100·0%)	410 (100·0%)	811 (100·0%)
Hospital admissions, n(%)	401 (100·0%)	410 (100·0%)	811 (100·0%)
Mortality, n(%)	401 (100·0%)	410 (100·0%)	811 (100·0%)
MRSA infection/colonisation, n(%)	395 (98·5%)	407 (99·3%)	802 (98·9%)
Clostridioides difficile infection, n(%)	394 (98·3%)	407 (99·3%)	801 (98·8%)
De-labelling outcomes, n(%)	389 (97·0%)	400 (97·6%)	789 (97·3%)

NB All participants that withdrew from follow-up had a prescription and a hospital admission before withdrawing, so there are no missing data for these participants for these outcomes.

Table S5 Completion of follow-up assessments, withdrawals, and lost to follow-up

	Penicillin allergy test	Usual clinical care	Overall
Expressed interest	-	-	1616
Attended eligibility appointment	-	-	1383
Assessment for eligibility and consented	-	-	950
Excluded (not randomised)	-	-	127
Randomised	411	412	823
Study assessments			
Participants in the study at 12 months	381	397	778
Participants completed 12-month CRF	301	307	608
Reasons for withdrew/Discontinued/LTFU*	30	15	45
Consent withdrawal	*3 (10·0%)*	*6 (40·0%)*	*9 (20·0%)*
Ineligibility†	*10 (33·3%)*	*2 (13·3%)*	*12 (26·7%)*
Significant protocol deviation	*0 (0·0%)*	*0 (0·0%)*	*0 (0·0%)*
Due to safety concern	*2 (6·7%)*	*0 (0·0%)*	*2 (4·4%)*
Lost to follow-up	*6 (20·0%)*	*3 (20·0%)*	*9 (20·0%)*
Other	*18 (60·0%)*	*7 (46·7%)*	*25 (55·6%)*
Included in analysis population	401	410	811
Data available for primary analysis	401	410	811
Included in as treated analysis population	365	446	811
Included in safety analysis population	365	446	811

NB Percentages for the withdrew/discontinued/lost to follow-up has been computed with the number of participants that either withdrew, discontinued, or were lost to follow-up.
*Can be more than one reasons.
†Participants found to be ineligible after randomisation and excluded from analysis population. LTFU= loss to follow-up after randomisation.
NB All participants that withdrew from follow-up had a prescription and a hospital admission before withdrawing, so there are no missing data for these participants for these outcomes

Table S6 Baseline characteristics by actual intervention received

	Received penicillin allergy test (N=365)	Received Usual Care (N=446)	Overall (N=811)
DEMOGRAPHICS & MINIMISATION FACTORS			
Age categories (Randomisation)			
18-64 years, n(%)	242 (66·3%)	312 (70·0%)	554 (68·3%)
65 years and older, n(%)	123 (33·7%)	134 (30·0%)	257 (31·7%)
Age (years)			
Mean (SD) [Range]	55·3 (15·8) [20·1 to 91·9]	54·8 (15·4) [19·8 to 85·3]	55·0 (15·6) [19·8 to 91·9]
Age categories (EudraCT guidelines)			
18-64 years, n(%)	243 (66·6%)	312 (70·0%)	555 (68·4%)
65-84 years, n(%)	119 (32·6%)	133 (29·8%)	252 (31·1%)
85 years and over, n(%)	3 (0·8%)	1 (0·2%)	4 (0·5%)
Gender			
Male, n(%)	99 (27·1%)	128 (28·7%)	227 (28·0%)
Female, n(%)	266 (72·9%)	318 (71·3%)	584 (72·0%)
Ethnicity*			
White†, n(%)	353 (98·1%)	433 (98·6%)	786 (98·4%)
Mixed or Multiple ethnic groups‡, n(%)	3 (0·8%)	2 (0·5%)	5 (0·6%)
Asian or Asian British§, n(%)	3 (0·8%)	3 (0·7%)	6 (0·8%)
Black, African, Caribbean or Black British¶, n(%)	1 (0·3%)	1 (0·2%)	2 (0·3%)
Other ethnic group‖, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Missing	*5*	*7*	*12*
Index of multiple deprivation quintile			
1 (Most deprived), n(%)	44 (12·1%)	47 (10·6%)	91 (11·3%)
2, n(%)	42 (11·6%)	58 (13·1%)	100 (12·4%)
3, n(%)	93 (25·6%)	105 (23·7%)	198 (24·6%)
4, n(%)	107 (29·5%)	132 (29·8%)	239 (29·7%)
5 (Least deprived), n(%)	77 (21·2%)	101 (22·8%)	178 (22·1%)
Missing	*2*	*3*	*5*
Number of antibiotics in the 24 months prior to recruitment (Randomisation)			
One, n(%)	240 (65·8%)	290 (65·0%)	530 (65·4%)
Two, n(%)	61 (16·7%)	71 (15·9%)	132 (16·3%)
Three, n(%)	27 (7·4%)	37 (8·3%)	64 (7·9%)
More than three, n(%)	37 (10·1%)	48 (10·8%)	85 (10·5%)
Number of antibiotic prescriptions in the 24 months prior to recruitment (SystmOne)			

	Received penicillin allergy test (N=365)	Received Usual Care (N=446)	Overall (N=811)
Mean (SD)	1·9 (1·5)	1·8 (1·6)	1·9 (1·6)
[Range]	[0·0 to 12·0]	[0·0 to 15·0]	[0·0 to 15·0]
Number of QOF (Randomisation)			
None, n(%)	68 (18·6%)	88 (19·7%)	156 (19·2%)
One - two, n(%)	195 (53·4%)	240 (53·8%)	435 (53·6%)
More than three, n(%)	102 (27·9%)	118 (26·5%)	220 (27·1%)
Number of QOF registered diseases (SystmOne)			
Mean (SD)	1·8 (1·4)	1·8 (1·4)	1·8 (1·4)
[Range]	[0·0 to 7·0]	[0·0 to 8·0]	[0·0 to 8·0]
EQ5D index value			
Mean (SD)	0·9 (0·2)	0·9 (0·2)	0·9 (0·2)
Median (IQR)	1·0 (0·8 to 1·0)	0·9 (0·8 to 1·0)	0·9 (0·8 to 1·0)
[Range]	[0·2 to 1·0]	[-0·2 to 1·0]	[0·2 to 1·0]
EQ5D VAS score			
Mean (SD)	80·2 (15·2)	79·4 (16·2)	79·7 (15·7)
Median (IQR)	80 (75 to 90)	80 (70 to 90)	80 (70 to 90)
[Range]	[7 to 100]	[10 to 100]	[7 to 100]
Testing Site			
Leeds, n(%)	274 (75·1%)	331 (74·2%)	605 (74·6%)
Leeds or BRI, n(%)	54 (14·8%)	62 (13·9%)	116 (14·3%)
Sheffield, n(%)	21 (5·8%)	34 (7·6%)	55 (6·8%)
Truro, n(%)	16 (4·4%)	19 (4·3%)	35 (4·3%)
SYSTMONE MEDICAL HISTORY			
Antibiotics prescriptions in the 12 months prior to recruitment			
Yes, n(%)	252 (69·0%)	311 (69·7%)	563 (69·4%)
No, n(%)	113 (31·0%)	135 (30·3%)	248 (30·6%)
Mean (SD)	1·3 (1·5)	1·4 (1·8)	1·4 (1·7)
[Range]	[0·0 to 8·0]	[0·0 to 15·0]	[0·0 to 15·0]
Antibiotics prescriptions in the 12-24 months prior to recruitment			
Yes, n(%)	111 (98·2%)	132 (96·4%)	243 (97·2%)
No, n(%)	2 (1·8%)	5 (3·6%)	7 (2·8%)
Mean (SD)	1·8 (1·6)	1·4 (1·0)	1·6 (1·3)
[Range]	[0·0 to 12·0]	[0·0 to 9·0]	[0·0 to 12·0]
Missing	*252*	*310*	*562*
QOF registered diseases**			
None, n(%)	68 (18·6%)	89 (20·0%)	157 (19·4%)

	Received penicillin allergy test (N=365)	Received Usual Care (N=446)	Overall (N=811)
Asthma, n(%)	45 (12·3%)	75 (16·8%)	120 (14·8%)
Atrial fibrillation, n(%)	6 (1·6%)	13 (2·9%)	19 (2·3%)
Blood pressure, n(%)	231 (63·3%)	277 (62·1%)	508 (62·6%)
Cancer, n(%)	41 (11·2%)	25 (5·6%)	66 (8·1%)
CHD, n(%)	16 (4·4%)	19 (4·3%)	35 (4·3%)
Chronic kidney disease, n(%)	17 (4·7%)	16 (3·6%)	33 (4·1%)
COPD, n(%)	12 (3·3%)	9 (2·0%)	21 (2·6%)
Dementia, n(%)	0 (0·0%)	1 (0·2%)	1 (0·1%)
Depression, n(%)	62 (17·0%)	76 (17·0%)	138 (17·0%)
Diabetes, n(%)	29 (7·9%)	29 (6·5%)	58 (7·2%)
Epilepsy, n(%)	4 (1·1%)	5 (1·1%)	9 (1·1%)
Heart failure, n(%)	4 (1·1%)	4 (0·9%)	8 (1·0%)
Hypertension, n(%)	83 (22·7%)	100 (22·4%)	183 (22·6%)
Learning disabilities, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Mental health, n(%)	2 (0·5%)	2 (0·4%)	4 (0·5%)
Obesity, n(%)	56 (15·3%)	84 (18·8%)	140 (17·3%)
Osteoporosis, n(%)	6 (1·6%)	1 (0·2%)	7 (0·9%)
PAD, n(%)	1 (0·3%)	2 (0·4%)	3 (0·4%)
Palliative care, n(%)	3 (0·8%)	0 (0·0%)	3 (0·4%)
Rheumatoid arthritis, n(%)	1 (0·3%)	7 (1·6%)	8 (1·0%)
Smoking, n(%)	15 (4·1%)	26 (5·8%)	41 (5·1%)
Stroke, n(%)	7 (1·9%)	12 (2·7%)	19 (2·3%)
PENICILLIN ALLERGY HISTORY (PATIENT REPORTED)			
How long have you been allergic to penicillin?			
<5 years, n(%)	19 (5·2%)	23 (5·2%)	42 (5·2%)
5-10 years, n(%)	16 (4·4%)	31 (7·0%)	47 (5·8%)
10-15 years, n(%)	27 (7·4%)	27 (6·1%)	54 (6·7%)
Over 15 years, n(%)	290 (79·5%)	358 (80·3%)	648 (79·9%)
Don't know, n(%)	13 (3·6%)	7 (1·6%)	20 (2·5%)
Penicillin that caused the allergic reaction[7]			
Penicillin V, n(%)	8 (2·2%)	17 (3·8%)	25 (3·1%)
Penicillin G, n(%)	2 (0·5%)	0 (0·0%)	2 (0·2%)
Ampicillin, n(%)	3 (0·8%)	7 (1·6%)	10 (1·2%)
Amoxicillin, n(%)	60 (16·4%)	60 (13·5%)	120 (14·8%)
Co-amoxiclav, n(%)	5 (1·4%)	13 (2·9%)	18 (2·2%)
Flucloxacillin, n(%)	10 (2·7%)	15 (3·4%)	25 (3·1%)
Piperacillin/tazobactam, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Temocillin, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Pivmecillinam, n(%)	0 (0·0%)	1 (0·2%)	1 (0·1%)
Don't know, n(%)	279 (76·4%)	334 (74·9%)	613 (75·6%)
Other, n(%)	3 (0·8%)	4 (0·9%)	7 (0·9%)
How was the penicillin that caused the allergic reaction taken?**			

	Received penicillin allergy test (N=365)	Received Usual Care (N=446)	Overall (N=811)
Oral (by mouth), n(%)	280 (76·7%)	326 (73·1%)	606 (74·7%)
Injection, n(%)	8 (2·2%)	16 (3·6%)	24 (3·0%)
Don't know, n(%)	78 (21·4%)	103 (23·1%)	181 (22·3%)
Missing	*0*	*2*	*2*
Allergic symptom[7]			
Red rash (affecting a large part of the body, no blistering, non itchy), n(%)	25 (6·8%)	31 (7·0%)	56 (6·9%)
Red rash (affecting a part of the body, no blistering, non itchy), n(%)	18 (4·9%)	30 (6·7%)	48 (5·9%)
Rash with blistering, n(%)	4 (1·1%)	7 (1·6%)	11 (1·4%)
Urticaria (red blotchy/itchy rash), n(%)	111 (30·4%)	120 (26·9%)	231 (28·5%)
Rash (no details known), n(%)	78 (21·4%)	105 (23·5%)	183 (22·6%)
Swelling of the face, n(%)	17 (4·7%)	13 (2·9%)	30 (3·7%)
Swelling of the tongue, n(%)	2 (0·5%)	2 (0·4%)	4 (0·5%)
Swelling of the hands, n(%)	3 (0·8%)	3 (0·7%)	6 (0·7%)
Swelling of other parts of the body, n(%)	10 (2·7%)	18 (4·0%)	28 (3·5%)
Difficulty breathing, n(%)	5 (1·4%)	4 (0·9%)	9 (1·1%)
Sneezing, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
Nausea, n(%)	16 (4·4%)	20 (4·5%)	36 (4·4%)
Vomiting, n(%)	31 (8·5%)	35 (7·8%)	66 (8·1%)
Abdominal discomfort or diarrhoea, n(%)	21 (5·8%)	31 (7·0%)	52 (6·4%)
Collapse - with loss of consciousness, n(%)	0 (0·0%)	2 (0·4%)	2 (0·2%)
Trush, n(%)	1 (0·3%)	4 (0·9%)	5 (0·6%)
Don't know/Can't remember, n(%)	72 (19·7%)	93 (20·9%)	165 (20·3%)
Other, n(%)	65 (17·8%)	86 (19·3%)	151 (18·6%)
How long after taking penicillin did you get the allergic reaction?			
After the first dose, n(%)	44 (12·1%)	59 (13·3%)	103 (12·8%)
During the course (after the second dose), n(%)	132 (36·2%)	151 (34·2%)	283 (35·1%)
After the course, n(%)	13 (3·6%)	5 (1·1%)	18 (2·2%)
Don't know, n(%)	176 (48·2%)	227 (51·4%)	403 (49·9%)
Missing	*0*	*4*	*4*
Did you consult with a doctor or attend an emergency department for the allergic reaction?			
Yes, n(%)	273 (74·8%)	329 (73·9%)	602 (74·3%)
No, n(%)	33 (9·0%)	35 (7·9%)	68 (8·4%)
Can't remember, n(%)	59 (16·2%)	81 (18·2%)	140 (17·3%)
Missing	*0*	*1*	*1*
Were you admitted to hospital?			
Yes, n(%)	9 (2·5%)	7 (1·6%)	16 (2·0%)
No, n(%)	318 (87·1%)	369 (82·9%)	687 (84·8%)

	Received penicillin allergy test (N=365)	Received Usual Care (N=446)	Overall (N=811)
Can't remember	38 (10·4%)	69 (15·5%)	107 (13·2%)
Missing	*0*	*1*	*1*
Do you have an allergic reaction to another group of antibiotics?			
Yes, n(%)	82 (22·5%)	103 (23·1%)	185 (22·8%)
No, n(%)	283 (77·5%)	343 (76·9%)	626 (77·2%)
OTHER SIGNIFICANT MEDICAL HISTORY (PATIENT REPORTED)			
Do you have any other medical condition?			
Yes, n(%)	260 (71·2%)	322 (72·2%)	582 (71·8%)
No, n(%)	105 (28·8%)	124 (27·8%)	229 (28·2%)
Are you pregnant or breast feeding?			
Yes, n(%)	0 (0·0%)	0 (0·0%)	0 (0·0%)
No, n(%)	365 (100·0%)	446 (100·0%)	811 (100·0%)
Are you currently taking any antihistamines?			
Yes, n(%)	42 (11·5%)	58 (13·0%)	100 (12·3%)
No, n(%)	323 (88·5%)	388 (87·0%)	711 (87·7%)
Are you currently taking or have you taken steroids within the last 10 days?			
Yes, n(%)	2 (0·5%)	3 (0·7%)	5 (0·6%)
No, n(%)	363 (99·5%)	443 (99·3%)	806 (99·4%)
Taking any other medication either prescribed by your GP or bought over the counter?			
Yes, n(%)	277 (75·9%)	346 (77·6%)	623 (76·8%)
No, n(%)	88 (24·1%)	100 (22·4%)	188 (23·2%)

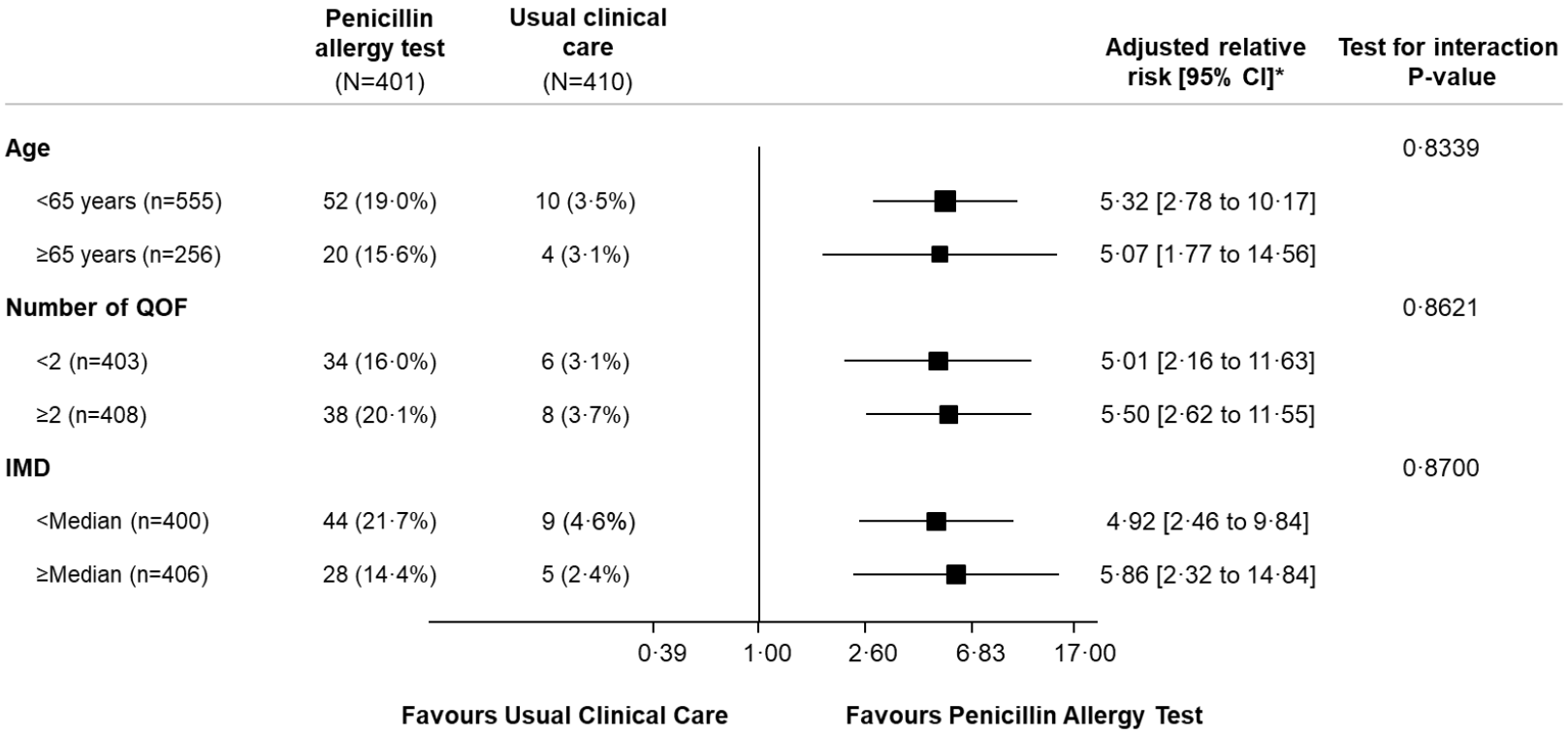
*NB Percentages have been computed with the number of participants with the response available as the denominator· *Collected from medical notes review. †Including British, Irish, Gypsy or Irish Traveller, and any other White background· ‡Including White and Black Caribbean, White and Black African, White and Asian, and any other Mixed or Multiple ethnic background. §Including Indian, Pakistani, Bangladeshi, Chinese, and other Asian background. ¶Including African, Caribbean, and other Black, African or Caribbean background. ‖Including Arab, and any other ethnic group. **Not mutually exclusive.*

Table S7 Sensitivity analyses in relation to the primary outcome

	Penicillin allergy test	Usual clinical care	Adjusted relative risk [95% CI] *	Adjusted risk difference [95% CI]	P-value†
As treated population‡, N	365	446			
Prescribed at least one course of a penicillin during follow-up, n(%)	72 (19·7%)	14 (3·1%)	6·37 [3·66 to 11·10]	16·3% [11·7% to 20·9%]	<0·0001
Excluding participants who did not have complete follow-up§, N	333	343			
Prescribed at least one course of a penicillin during follow-up, n(%)	62 (18·6%)	11 (3·2%)	5·71 [3·07 to 10·64]	15·0% [10·3% to 19·7%]	<0·0001
Excluding participants who had delayed PAAP§	379	410			
Prescribed at least one course of a penicillin during follow-up, n(%)	69 (18·2%)	14 (3·4%)	5·39 [3·09 to 9·39]	14·5% [10·1% to 18·9%]	<0·0001

*Penicillin allergy test versus Usual clinical care. †Level of statistical significance = 0·05. ‡Logistic mixed effects regression model adjusted for 'as treated' group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. A risk difference greater than 0 indicates improvement in favour of penicillin allergy test. A relative risk greater than 1 indicates improvement in favour of penicillin allergy test. §Logistic mixed effects regression model adjusted for randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. A risk difference greater than 0 indicates improvement in favour of penicillin allergy test. A relative risk greater than 1 indicates improvement in favour of penicillin allergy test.
SD = standard deviation.

Figure S2 Subgroup analysis of primary outcome



* Penicillin allergy test versus Usual clinical care. Logistic mixed effects regression model adjusted for randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), the number of QOF registered disease, and an interaction between randomisation group and subgroup indicator as fixed effects, and GP practice as a random effect. A relative risk greater than 1 indicates improvement in favour of penicillin allergy test. †Level of statistical significance = 0·05.

Table S8 Penicillin prescribed to participants in the Penicillin allergy test group

Antibiotic	Number of penicillin prescriptions for primary events*
Amoxicillin	48
Co-amoxiclav	4
Flucloxacillin	25
Phenoxymethylpenicillin	17
Total	94

* not mutually exclusive (i.e. patients could have more than one penicillin prescribed)

Table S9 Antibiotic prescribing data by antibiotic class/agent

	Penicillin allergy test	Usual clinical care
Received a prescription for a cephalosporin class antibiotic, n/N (%)	7/401 (1·7%)	17/410 (4·1%)
Number of prescriptions, Mean (SD)	1·1 (0·4)	2·2 (1·1)
Number of days of prescriptions, Mean (SD)	11·7 (8·3)	34·3 (63·9)
Defined daily dose for prescription, Mean (SD)	3·1 (2·2)	6·0 (7·7)
Received a prescription for a tetracycline class antibiotic, n/N (%)	46/401 (11·5%)	71/410 (17·3%)
Number of prescriptions, Mean (SD)	1·4 (0·7)	1·5 (0·9)
Number of days of prescriptions, Mean (SD)	18·6 (22·7)	19·3 (34·9)
Defined daily dose for prescription, Mean (SD)	17·3 (19·7)	18·5 (25·5)
Received a prescription for a fluoroquinolone class antibiotic, n/N (%)	0 (0·0%)	0 (0·0%)
Received a prescription for a macrolide class antibiotic, n/N (%)	35/401 (8·7%)	82/410 (20·0%)
Number of prescriptions, Mean (SD)	1·2 (0·5)	1·8 (1·7)
Number of days of prescriptions, Mean (SD)	9·3 (5·8)	24·9 (56·4)
Defined daily dose for prescription, Mean (SD)	8·8 (4·5)	20·1 (40·7)
Received a prescription for a glycopeptide class antibiotic, n/N (%)	2/401 (0·5%)	3/410 (0·7%)
Number of prescriptions, Mean (SD)	1·0 (0·0)	2·3 (1·5)
Number of days of prescriptions, Mean (SD)	1·0 (0·0)	10·0 (7·9)
Defined daily dose for prescription, Mean (SD)	1·0 (0·0)	16·2 (15·4)
Received a prescription for an aminoglycoside class antibiotic, n/N (%)	2/401 (0·5%)	1/410 (0·2%)
Number of prescriptions, Mean (SD)	1·0 (0·0)	1·0 (-)
Number of days of prescriptions, Mean (SD)	1·0 (0·0)	1·0 (-)
Defined daily dose for prescription, Mean (SD)	0·6 (0·1)	0·5 (-)
Received a prescription for a oxazolidinone class antibiotic, n/N (%)	0/401 (0·0%)	1/410 (0·2%)
Number of prescriptions, Mean (SD)	-	1·0 (-)
Number of days of prescriptions, Mean (SD)	-	2·0 (-)
Defined daily dose for prescription, Mean (SD)	-	1·0 (-)
Received a prescription for a monobactam class antibiotic, n/N (%)	0/401 (0·0%)	2/410 (0·5%)
Number of prescriptions, Mean (SD)	-	1·0 (0·0)
Number of days of prescriptions, Mean (SD)	-	3·5 (3·5)
Defined daily dose for prescription, Mean (SD)	-	1·8 (1·8)
Received a prescription for a carbapenem class antibiotic, n/N (%)	0/401 (0·0%)	2/410 (0·5%)
Number of prescriptions, Mean (SD)	-	1·0 (0·0)
Number of days of prescriptions, Mean (SD)	-	3·0 (1·4)

	Penicillin allergy test	Usual clinical care
Defined daily dose for prescription, Mean (SD)	-	1·0 (0·5)
Received a prescription for fosfomycin, n/N (%)	4/401 (1·0%)	6/410 (1·5%)
Number of prescriptions, Mean (SD)	1·2 (0·5)	1·0 (0·0)
Number of days of prescriptions, Mean (SD)	2·5 (1·0)	3·0 (2·4)
Defined daily dose for prescription, Mean (SD)	2·5 (1·0)	3·0 (2·4)
Received a prescription for nitrofurantoin, n/N (%)	43/401 (10·7%)	52/410 (12·7%)
Number of prescriptions, Mean (SD)	1·7 (1·0)	1·6 (1·4)
Number of days of prescriptions, Mean (SD)	12·1 (17·1)	16·9 (35·8)
Defined daily dose for prescription, Mean (SD)	5·7 (8·6)	7·2 (11·4)
Received a prescription for trimethoprim, n/N (%)	13/401 (3·2%)	14/410 (3·4%)
Number of prescriptions, Mean (SD)	1·3 (0·5)	1·4 (0·9)
Number of days of prescriptions, Mean (SD)	8·3 (5·8)	16·1 (29·1)
Defined daily dose for prescription, Mean (SD)	4·2 (2·9)	6·4 (7·0)
Received a prescription for trimethoprim, n/N (%)	0/401 (0·0%)	0/410 (0·0%)
Received a prescription for rifampicin, n/N (%)	0/401 (0·0%)	0/410 (0·0%)
Received a prescription for colistin, n/N (%)	0/401 (0·0%)	0/410 (0·0%)
Received a prescription for metronidazole, n/N (%)	0 (0·0%)	0 (0·0%)

SD = standard deviation

Table S10 Exploratory hospital analyses

	Penicillin allergy test	Usual clinical care	Adjusted Treatment Effect [95% CI]*	P-value†
Admitted to hospital during the 12-month trial period, n/N (%)	30/401 (7·5%)	31/410 (7·6%)	0·99 [0·62 to 1·60]‡	0·9827
Number of hospital admissions during the 12-month trial period, Mean (SD) [n]	2·4 (2·4) [30]	1·9 (1·2) [31]	1·32 [0·93 to 1·87]§	0·1162
Length of hospital stay (days) for admissions during the 12-month trial period, Median (IQR) [n]	2·0 (1·0 to 5·0) [30]	3·0 (1·0 to 8·0) [31]	-0·81 [-3·65 to 2·03]ll	0·5699

* Penicillin allergy test versus Usual clinical care. †Level if statistical significance = 0·05. ‡Logistic mixed effects regression model adjusted for randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. Ah adjusted relative risk less than 1 indicates improvement in favour of penicillin allergy test. §Poisson mixed effects regression model adjusted for randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. A indicate rate ratio less than 1 indicates improvement in favour of penicillin allergy test. llQuantile regression model adjusted for randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation. SD = standard deviation

Table S11a Summary of safety outcomes (as treated population)

	Penicillin allergy test	Usual clinical care	P-value*
Number of participants experienced an adverse event (AE), n	**365**	**446**	-
None	292 (80·0%)	446 (100·0%)	
1	65 (17·8%)	0 (0·0%)	
2	6 (1·6%)	0 (0·0%)	
3	2 (0·5%)	0 (0·0%)	
>3	0 (0·0%)	0 (0·0%)	
Intensity of adverse events, n(%)	**83**	**0**	-
Mild	72 (86·7%)	-	
Moderate	10 (12·0%)	-	
Severe	1 (1·2%)	-	
Causality of adverse event, n(%)	**83**	**0**	-
Not related	9 (11·0%)	-	
Possibly related	15 (18·3%)	-	
Probably related	51 (62·2%)	-	
Definitely related	7 (8·5%)	-	
Unknown	0 (0·0%)	-	
Experienced a serious adverse event	**365**	**446**	0·6244
None	338 (92·6%)	412 (92·4%)	
1	22 (6·0%)	31 (7·0%)	
2	3 (0·8%)	2 (0·4%)	
3	1 (0·3%)	0 (0·0%)	
>3	1 (0·3%)	1 (0·2%)	

*Fisher's exact test. Level of significance = 0·05. SD = standard deviation

Table S11b Summary intensity of adverse events by causality

	Intensity of adverse events		
Causality of adverse event	**Mild**	**Moderate**	**Severity**
Not related	9	0	0
Possibly related	14	1	0
Probably related	45	5	1*
Definitely related	3	4	0
Unknown	1	0	0

* Gastro-oesophageal reflux

Table S12: Adverse reactions to penicillin allergy test (Day 4-6 questionnaire)

Reaction to Penicillin allergy test	Result positive (N=30)
Red rash (affecting a large part of the body, no blistering, non itchy), n(%)	3 (10·0%)
Red rash (affecting a part of the body, no blistering, non itchy), n(%)*	6 (20·0%)
Rash with blistering, n(%)	1 (3·3%)
Urticaria (red blotchy/itchy rash), n(%)	14 (46·7%)
Rash (no details known), n(%)	1 (3·3%)
Swelling of the face, n(%)abxused†	3 (10·0%)
Swelling of the tongue, n(%)	0 (0·0%)
Swelling of the hands, n(%)	1 (3·3%)
Swelling of other parts of the body, n(%)	1 (3·3%)
Difficulty breathing, n(%)	1 (3·3%)
Sneezing, n(%)	1 (3·3%)
Nausea, n(%)	1 (3·3%)
Vomiting, n(%)	0 (0·0%)
Abdominal discomfort or diarrhoea, n(%)	1 (3·3%)
Collapse - with loss of consciousness, n(%)	0 (0·0%)
Thrush, n(%)	0 (0·0%)
Other, n(%)	2 (6·7%)

NB Percentages have been computed with the number of participants with the response available as the denominator. Reactions are not mutually exclusive, i.e participants could have had more than one at the same time.
* One participant took Co-Amoxiclav, † One participant took Flucloxacillin, and the remaining participants with reactions took Amoxicillin

Health economic evaluation (within trial analysis)

Summary

Aim

The aim of this study was to conduct an economic evaluation of the cost-effectiveness of the penicillin allergy test pathway intervention versus usual care from the perspective of the National Health Service (NHS) and personal social services (PSS) in England. This was done on a within-trial basis, using up to 12 months of follow-up in the ALABAMA RCT.

Background

No previous study has investigated the effects of penicillin allergy testing on patient reported outcomes in the setting of a RCT. We present an evaluation of the effects of penicillin allergy test on costs, patient health related quality of life and cost-effectiveness in patients recruited to the ALABAMA RCT. Details of the health economic analysis plan, which includes extended analyses beyond the end of the trial being published separately, are available publicly: ISRCTN20579216 HEALTH ECONOMICS ANALYSIS PLAN_ALABAMA_v1.15 17Jun2024.pdf.

Methods

We followed the National Institute for Health and Care Excellence's (NICE) reference case to conduct a cost-utility analysis (NICE 2012). We present data on incremental costs from a health and personal social service provider perspective, including the costs of the intervention, from a micro-costing analysis using data collected in the trial, and primary and secondary health care service use, using individual participant data on penicillin allergy testing and health-related quality of life collected during the trial, and linked information from administrative sources. A summary of trial and linked data used in the analysis is presented in Table S13. We adopt willingness to pay thresholds of £20,000 (GBP) and £30,000 per QALY.

Table S13 Data sources, outcomes and time points available for the health economic evaluation of penicillin allergy test pathway

	Assessment						
Measure	**Baseline**	**Day0 (day of allergy test)**	**Day 4-6 post penA test**	**2-4 days post Ab prescription**	**28-30 days post Ab prescription**	**Month 12**	**Month 12+ up to 54 months**
Trial participant characteristics Minimisation factors and randomisation	✓						
Penicillin allergy test Resources involved in testing for penicillin allergy test arm		✓	✓				
Follow-up Penicillin allergy test Health care service use			✓				
EQ-5D-5L Measures utility scores.	✓			✓	✓	✓	
Primary care resource utilisation data Linked to electronic Health Records (SystmOne, Open Clinica) and case note reviews: Index antibiotic medications (see ALABAMA Study Protocol) and GP and Nurse-led consultations. Ongoing data collection*		✓	✓	✓	✓	✓	✓
Secondary care resource utilisation and survival Linked to HES (Admitted Patient Care, Outpatient, Critical Care), Emergency Care Data Set, Civil Registrations of Death. Through HES APC, Ab prescriptions during hospital admissions collected from review of hospital notes. Ongoing data collection†		✓	✓	✓	✓	✓	✓

*Up to end of November 2023; †Up to April 2024. Ab, antibiotic; GP, general practitioner; HES, hospital episode statistics.

Methods of Analysis for the economic evaluation of the cost-effectiveness of penicillin allergy test

The initial cost-effectiveness analysis of penicillin allergy test presented here is based on within-trial outcomes. Costs used in the analysis were measured using linked administrative data from baseline to 12 months, whilst health-related quality of life (HRQoL) data were collected from trial participants at baseline and a planned date of one year later[1], as well as 2-4 days and 28-30 days after a primary event. Due to the one-year time horizon, costs and benefits are not discounted.

Health Benefits

HRQoL of trial participants was measured using the EQ-5D-5L measure, mapped into the EQ-5D-3L index score (utility) values using a published cross walk as per the current NICE position statement (NICE 2019). Full details of the method adopted for converting utility values to an estimate of QALYs are provided in the Health Economics Analysis Plan. Briefly, the mapped EQ-5D utility scores were combined with information of date of death for any patients deceased over the period of analysis to derive QALYs using the area under the curve method. We adopted a number of different statistical models for estimating differences in QALYs and costs by treatment arm in order to test the robustness of our results to plausible changes in best methodological practice. We use the output of these models to provide point estimates of such differences, and from these construct estimates of the incremental cost-effectiveness ratio (ICER) and incremental net health benefit (NHB) and net monetary benefit (NMB). Incremental NHB is given by the following formula using the £20,000 or £30,000 NICE cost-effectiveness threshold (CET) :

$$\text{Incremental NHB} = (\text{QALYs}_{\text{penicillin allergy test}} - \text{QALYs}_{\text{usual care}}) - \left(\frac{\text{Costs}_{\text{penicillin allergy test}} - \text{Costs}_{\text{usual care}}}{\text{CET}}\right)$$

whilst incremental NMB was calculated as:

$$\text{Incremental NMB} = \text{CET} \times (\text{QALYs}_{\text{penicillin allergy test}} - \text{QALYs}_{\text{usual care}}) - (\text{Costs}_{\text{penicillin allergy test}} - \text{Costs}_{\text{usual care}})$$

Using mean QALYs and mean costs, the incremental NHB measures net benefit in terms of per patient QALY units, whereas the NMB presents the equivalent results in terms of per patient GBP.

[1]In practice there was some variation around this date of final follow-up. Five percent of participants included in the analysis and with available data (811) had their final EQ-5D measured at 308 days or less from baseline and, at the opposite end of the distribution, for 5% of these patients it exceeded 425 days. In our primary analysis, as commonly practiced, we present results assuming that 365 days passed between the baseline and final follow-up questionnaire being conducted. We account for this shorter length of follow-up in a sensitivity analysis.

Costs

Intervention

The costs of the penicillin allergy test intervention were calculated using retrospective data on the staff time inputs into penicillin allergy test at Leeds and Truro allergy testing study clinic sites, including time receiving training and delivering screening, risk stratification and testing (by skin test and/or oral challenge), and time spent by allergy specialists training staff delivering penicillin allergy test. Use of medications and consumables were imputed based on standard operating procedures for penicillin allergy test, which align with standard testing procedures in routine practice at the allergy testing clinic of the Leeds Teaching Hospitals NHS Trust. The staff time inputs into delivering penicillin allergy test were validated using prospectively collected data at the Leeds allergy clinic for two cases in the study, one of a trial participant in the intervention arm who received skin prick testing (SPT) with intradermal test (IDT) and oral challenge test (OCT) and another participant who was tested using direct OCT. In addition, prospective data collected from electronic records for the testing start and end time for each of SPT, IDT and OCT from Bradford (n=13) and Leeds (n=10) were used to cross-validate the reported duration of penicillin allergy test activities in the retrospective proforma. Staff time inputs were valued according to Title and Grade using 2022-2023 Personal Social Services Research Unit (PSSRU) unit costs for clinical and non-clinical professional staff (Jones et al. 2024) and Agenda for Change 2023 salaries with on costs for administrative staff. Antibiotic medications used in penicillin allergy test were assigned hospital acquisition prices from the eMIT database (accessed February 2024). Since each of the four study allergy testing centres used a different mix of staff skills to deliver penicillin allergy test, we valued the staff time inputs according to such differences. Table S14 presents the resource inputs for the Leeds allergy testing centre, which conducted the bulk of the penicillin allergy testing in the study. The costs of testing for high and low risk patients are presented in Table S15 by study testing centre.

Table S14 Costs elements of penicillin allergy test

Input	Quantity	Unit	Unit cost (£)	Cost (£)	Source	Calculation and comments
0. Access to SystmOne	Annual fee	NA	NA	NA	Private Company information	Calculated using annual charge to access and receive training divided over the eligible ALABAMA patient population across the 7 regions of the UK
1. Training (Trainer's time)	6·00	hour	0·22	2·71	PSSRU 2023; Band 6 allergy nurse	Retrospective data from Truro; 3 years' service to 50 tests per year; 3·5% annual discount rate
2. Searches in SystmOne & screening	0·08	hour	29	2·36	https://nhspayscales.co.uk/ Admin Band 3, with on costs; PSSRU 2023 Pharmacist Band 6	30 min to set up & run 2 searches; 2 x 10 min pharmacist appointments to screen lists divided by 823* trial participants
3. Contact to book appointment	0·12	hour	20	2·37	https://nhspayscales.co.uk/ Admin Band 3 2023/24, with on costs	Retrospective data from Leeds; Telephone and text message contact
4. Liaise with patient to check availability	0·05	hour	58	2·90	PSSRU 2023; Nurse Band 6	Retrospective data from Leeds
5. Risk stratification	0·27	hour	74	20·02	PSSRU 2023; 75% Nurse Band 6, 25% Clinical Fellow ST5	Retrospective data from Leeds. Includes allergy specialist input, 10 min in 61 out of 308 of cases.
6. Explain test to patient	0·08	hour	63	5·28	PSSRU 2023; Nurse Band 6.	Prospective data collected from Leeds (n=3) and Bradford (n=18)
7. Skin test (SPT+ IDT)	1·09	hour		74·17		
8. Oral challenge test (OCT)	1·10	hour		69·76		
9. Skin test (SPT+ IDT) drugs	2·00	vials	0·45	0·92	eMIT database	2x amoxicillin 250mg powder for solution for injection vials (Packsize 10)
10. Skin test (SPT + IDT) consumables	·	·	·	8·83	LTHT supplies purchasing data, online medical supplier data	Histamine controls; 0·9% sodium, lancets, skin marker; SPT metal box for 56 vials; supply delivery, 30G Needle, syringe, gloves

Input	Quantity	Unit	Unit cost (£)	Cost (£)	Source	Calculation and comments
11. OCT drugs	4.00	dose	0·75	3·00	eMIT database	Amoxicillin 125mg/5ml oral suspension sugar free 100 ml / Packsize 1
12. Follow-up care (if received OCT)	0·25	hour	63	15·85	PSSRU 2023; 75% Nurse Band 6, 25% Clinical Fellow ST5	Prospective data collected from Leeds (n=3)
13. Transfer results for & check draft letter, remind GP to update record	0·27	hour	49	13·15	PSSRU 2023; 50% Nurse Band 6, 50% Clinical Trial Assistant B5	Retrospective data from Leeds study site.
14. Updating hospital records	0·01	hour	78	0·42	PSSRU 2023; Clinical Fellow ST5	Retrospective data from Leeds: updating of 49 out of 308 records in study site times 2 minutes
15. Draft & send results letter	0·50	Hour	21	10·49	https://nhspayscales.co.uk/ Administrative staff Band 4; Predicted 2023/24 salary; Includes on costs	Retrospective data collected from Leeds study site.

NA: Information is Redacted as Commercial In Confidence.
* Includes 10 individuals randomised in ALABAMA who were later deemed to be ineligible and withdrawn from the study, as these would be expected to occur in routine practice. GP, general practitioner; IDT, intradermal test; LTHT, Leeds Teaching Hospitals NHS Trust; PSSRU 2023, Personal Social Services Research Unit, Unit Costs of Health and Social Care Manual 2023 (Jones et al. 2024); ST, specialty trainee; SPT, skin prick test.

Table S15 Unit s of penicillin allergy test by test in study allergy centres

Test	Allergy centre				Comments
	Leeds	Sheffield	Bradford	Truro	
SPT + OC	234	218	272	324	Includes cost of SystmOne access and training, screening, risk stratification, Training, Staff, medications and consumables
SPT	137	129	158	177	
OC	155	145	179	210	

Note: Estimated from antibiotic medications, consumables and staff time inputs into penicillin allergy test delivery at the Leeds allergy centre, valued at staff time cost per hour according to the Title and Grade of staff delivering the intervention at each centre. SPT=skin prick test; OC = oral challenge

Health care service use

In line with the 12-month duration of the within trial period, resource use was included in the analysis if it occurred between the date of baseline questionnaire completion and 365 days later. See Table S16 for a summary of identification and value sources.

Table S16 Resource use identification and value sources

Resource	Resource use source	Value source	Unit cost notes
Primary care			
Primary care consultations	OpenClinica database	PSSRU 2023	Weighted average of unit cost for General Practitioner and Practice nurse, for a consultation with duration 9·22mins. National estimates for ratio of GP:nurse appointments from NHS England*
Primary care antibiotics	SystmOne and Notes review	the NHS Drug Tariff costs 2023	These two datasets for resource use were merged, and where duplicates were found, we gave preference to information from SystmOne.
Secondary care			
Admitted inpatient stays (ward and critical care)	Hospital Episode Statistics	NHS Cost Collection 2021-2022, NHS Reference Costs 2017-18	Unit costs based on length of hospital stay and initial admission
Attendances to Outpatient department	Hospital Episode Statistics	NHS Cost Collection 2022	Health Resource Groups 2022
Attendances to Emergency department	Hospital Episode Statistics	NHS Cost Collection 2022	Health Resource Groups, HRG Grouper 2022
Other			
Death data	ONS	-	

*NHS England/Data/Publications/Appointments in General Practice, April 2022; PSSRU 2023, Personal Social Services Research Unit, Unit Costs of Health and Social Care Manual 2023 (Jones et al. 2024)

Hospital inpatient stays can be costed using 'Healthcare Resource Groups'(HRGs) which are allocated to each admission through the NHS Grouper Software. For each respective HRG, and the admission's 'type' (referring

to day case, elective, short-stay, or long-stay), a unit cost can be allocated using the costs published in the NHS Cost Collection. This is intended to represent a full absorption cost estimate, including direct costs (attributable to the patient's stay, such as ward staffing relevant to the patient, and, in the specific case of ALABAMA, any antibiotic usage), indirect costs and overhead costs.

While these costing datasets represent the best overall information regarding the costs of a stay in hospital, where this method is used with no adjustment, an individual's inpatient cost is relatively insensitive to their length of stay (LOS). Consequently, within a research trial setting an intervention's effect on inpatient LOS may not be sufficiently reflected in the calculated HRG-cost difference between trial arms. In order to capture the effect that removing an incorrect penicillin allergy label may have on patient care, both through enabling 'first- line' treatment and possibly eliminating the observed increased duration of hospital stays associated with a penicillin allergy label (Powell et al. 2020), we developed an inpatient-costing approach which incorporates both the HRG-specific unit costs and an individual's LOS. Therefore, in our approach to costing, admissions that are day-cases or non-elective short-stays (0- and 1-day duration respectively) directly take the corresponding HRG unit cost (no specific LOS adjustment is made for these; NHSCC 2022). For admissions that are longer than 1-day duration, we calculated a 'fixed' unit cost for the first day of admission, and an additional per-diem cost for any inpatient days >1. To estimate the initial fixed cost and per-diem cost for each HRG/Admission-type (HRG-AT), we considered the national average LOS for each HRG-AT, respective admission-type excess bed day cost and the standard HRG-AT unit cost (NHSCC 2018, 2017-18 is the most recent year for which published data exists).

Costing of outpatient attendances and the Emergency department was based on HRGs, which were constructed using OPCS4, ICD10 code and admission data for each patients using the HRG grouper. unit costs of the respective HRGs were obtained from the National Cost Collection 2021-2022.
Antibiotic medication use in primary care was obtained from SystmOne, supplemented by information from manual medication notes review, and evaluated using the NHS Drug Tariff for 2023. Information on consultations was obtained from electronic health records through the OpenClinica database and valued by type (GP and Nurse-led) using national unit cost estimates (PSSRU 2023).

The early termination of the ALABAMA trial led to some patients being followed-up for less than 365 days and additionally led to variation in observation time for resource use. Different periods under observation arise at an individual level for each of primary care and secondary care data. Both time periods could differ from the time period between baseline and final questionnaire. Data for secondary care from Hospital Episode Statistics (HES) was collected up to the end of November 2023, with 258 trial participants not having reached a year under observation at this point. In some cases, this divergence from a year was substantial: the first patient was lost to observation by month two, and 199 patients were lost to observation by month 10. Data for primary care resource use was collected up to the end of March 2024: while this led to fewer participants having censored resource use data, there still remained 70 whose period under observation was under one year. Table S17 and Table S18 summarises the extent of this censoring of cost data for each of these two categories,

giving a count of the number of trial participants who had been lost to observation by month from the start of their participation in the trial.

Table S17 Available data from linked electronic HES secondary care records by month

	Penicillin allergy test (n=401)		Usual care (n=410)		All (N=811)	
Month	**Frequency by month**	**Cumulative percentage by month**	**Frequency by month**	**Cumulative percentage by month**	**Frequency by month**	**Cumulative percentage by month**
1	0	0·00%	0	0·00%	0	0·00%
2	0	0·00%	1	0·25%	1	0·12%
3	0	0·00%	0	0·25%	0	0·12%
4	0	0·00%	3	1·00%	3	0·49%
5	2	0·50%	4	2·00%	6	1·23%
6	8	2·49%	4	2·99%	12	2·71%
7	10	4·99%	7	4·74%	20	5·18%
8	16	8·98%	16	8·73%	32	9·12%
9	27	15·71%	10	11·22%	50	15·29%
10	34	24·19%	41	21·45%	75	24·54%
11	24	30·17%	23	27·18%	46	30·21%
12	5	31·42%	6	28·68%	11	31·57%

Table S18 Available data from linked electronic primary care records by month

	Penicillin allergy test (n=401)		UCC (n=410)		All (N=811)	
Month	**Frequency by month**	**Cumulative percentage by month**	**Frequency by month**	**Cumulative percentage by month**	**Frequency by month**	**Cumulative percentage by month**
1	0	0·00%	0	0·00%	0	0·00%
2	0	0·00%	0	0·00%	0	0·00%
3	0	0·00%	0	0·00%	0	0·00%
4	0	0·00%	0	0·00%	0	0·00%
5	0	0·00%	0	0·00%	0	0·00%
6	0	0·00%	1	0·25%	1	0·12%
7	0	0·00%	0	0·25%	0	0·12%
8	0	0·00%	3	1·00%	3	0·49%
9	1	0·25%	3	1·75%	4	0·99%
10	9	2·49%	5	2·99%	14	2·71%
11	6	3·99%	7	4·74%	13	4·32%
12	17	8·23%	18	9·23%	35	8·63%

Missingness

Beyond variation in time under observation, no missingness exists in the resource use data. As such, no imputation of this category of data is undertaken, and no aspect of the costs data involves multiple imputation

methods. Where the date of the final EQ-5D-5L questionnaire is missing, a date 365 days on from baseline is assumed.

More advanced methods are required to deal with missingness in estimates of HRQoL. All observations are complete at baseline for both the questionnaire date and all dimensions of the EQ-5D-5L, and consequently, for the associated HRQoL estimate derived therefrom. However, substantial missingness is exhibited in both the end-of-trial measure of this and in components of HRQoL measures associated with any primary events, as well as the dates of such primary events. While up to six EQ-5D-5L questionnaires associated with primary events were completed per individual, this number varies substantially by individual.

As such, for almost all trial participants, there is a substantial number of such potential observations that are correctly missing according to the design of the study, as they had fewer than six primary events in the period under observation. However, where we have a date of questionnaire or a record of EQ-5D-5L responses for either or both the 2-4 day and/or 28-30 day questionnaires, we regard any unrecorded components of this as missing. As EQ-5D-5L dimensions are only ever entirely rather than partially missing, we impute the overall utility score derived from the crosswalk valuation rather than each individual dimension. We impute values by trial arm, where necessary, for any such variables, employing multiple imputation by kernel nearest neighbour predictive mean matching (Faria et al. 2014). In this imputation model, we use as covariates baseline utility and the battery of categorical variables (grouped age, grouped number of antibiotics, grouped number of QOF conditions, and GP practice) specified in the statistical analysis plan.

Sensitivity Analyses

We present separate sensitivity analyses to test the robustness of results to a series of unit cost and measurement assumptions:

i. Cost of penicillin allergy test at the day case HRG tariff (Tretspef code 313: Clinical immunology and allergy, £368)
ii. ‘As treated’ analysis, where patients randomised to penicillin allergy test who end up receiving no testing are reassigned to the control group
iii. Evaluate penicillin allergy test costs at the micro-costs estimates of the Leeds Immunology centre
iv. Exclude any health care resource use data from analysis that occur beyond a 56 day window after a primary event (recorded use of an index antibiotic prescription

Statistical methods

As our primary method, we estimate separate mixed effects models for costs and QALYs, in line with the statistics analysis plan, including fixed effects for grouped age, grouped number of antibiotics at baseline, grouped number of QOF conditions at baseline, as well as random effects for GP practices, additionally including baseline EQ-5D index score in our model for QALYs. Results from this method are presented in rows labelled “Mixed effects” in the tables below.

We thoroughly test the implications of these functional forms in sensitivity analyses. These sensitivity analyses involve:

(1) A model with all measured costs, assumed to be collected as a total on an annual basis, included as an equation, alongside an equation for QALYs, in a system fit using seemingly unrelated regression (Willan et al. 2004), with principal components factors used as covariates (Jolliffe et al. 1982). This method ignores the effect of censoring in observed data from patients who do not complete 12 months of follow-up. Results from this method are presented in rows labelled "seemingly unrelated regression" in the tables.

(2) A method that adjusts for incomplete censored follow-up data using the partitioned estimator (Chen et al. 2024). Results from this method are presented in rows labelled "Partitioned estimator" in the tables below.

We fit a series of monthly regression models for two categories of cost data using seemingly unrelated regression, sum the overall coefficient estimates for an overall estimate of cost difference, and use the obtained variance-covariance matrix to derive standard errors. In addition, a QALY equation is included in this system of equations fitted using seemingly unrelated regression. This allows us to estimate cost differences between treatment groups in each month from the first to the twelfth, using only individuals not yet censored at each timepoint, while also allowing for correlation between the error terms in different categories of costs across time. This makes efficient use of all available information about costing and allows constructing an unbiased point estimate of the difference in costs by treatment group.

The construction of the variance-covariance matrix required by seemingly unrelated regression becomes problematic with a large number of variables, particularly categorical variables with many levels, such as the number of GP practices. We used principal components analysis to reduce the dimensionality of our data, creating four factors from the categorical variables used as controls (grouped age, grouped number of antibiotics, grouped number of QOF variables, and GP practice) in the statistical analysis plan.

Analysis of uncertainty

Confidence intervals were obtained using the percentile bootstrap method. We take 10,000 random draws from the QALYs and costs differences in the analysis sample of ALABAMA trial participants to illustrate the uncertainty around our ICER and incremental NHB and NMB estimates and summarise this using the implied probability of cost-effectiveness at thresholds of £20,000 and £30,000. The chosen number of boostrap replications is more than twice the 1000-3000 replications that are typically found to provide stable bootstrap estimates (Briggs et al. 1997; Hunink et al. 1998; Efron and Tibshirani 1993). We further display this uncertainty graphically using cost-effectiveness planes to illustrate the distribution of estimated incremental costs and QALYs, and cost-effectiveness acceptability curves (CEACs) to illustrate how the probability of cost-effectiveness varies with the threshold value (Fenwick et al. 2001).

Results

Baseline characteristics in the sample for the ITT and As Treated analysis are presented in Table S19. The between trial arm difference in mean baseline EQ-5D index score (0.03) was 17% of one standard deviation.

Table S19 Baseline characteristics for intention to treat and as treated analyses

	ITT		As Treated	
	Penicillin allergy test n=401	Usual care n=410	Penicillin allergy test n=365	Usual care n=446
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Number of antibiotics	1.91 (1.51)	1.84 (1.65)	1.91 (1.51)	1.85 (1.64)
Age	54.35 (15.92)	54.67 (15.31)	54.81 (15.85)	54.27 (15.42)
Gender (% male)	27%	29%	27%	29%
Baseline EQ-5D index score	0.88 (0.16)	0.85 (0.19)	0.88 (0.16)	0.86 (0.18)
Number of QOF conditions	1.73 (1.42)	1.78 (1.40)	1.75 (1.44)	1.76 (1.38)

Thirty-six (9%) patients randomly allocated to the penicillin allergy test arm did not receive testing. The mean costs of penicillin allergy test per patient in the ITT analysis was £170 per patient (Table S20). In the group of patients who did receive penicillin allergy test the costs were slightly skewed to the right due to the smaller proportion of patients who were deemed of high enough risk to receive the full pathway of SPT + OC than those who received direct OC.

Table S20 Intervention costs, unadjusted means

	As treated		ITT	
	Penicillin allergy test n=365		Penicillin allergy test n=401	
Variable	**Mean (SD)**	**Median (IQR)**	**Mean (SD)**	**Median (IQR)**
penicillin allergy test test	186.23 (41.36)	155.13 (155.13 to 234)	169.52 (66.31)	155.13 (155.13 to 233.76)

Over the within trial period there was a mean of 0.25 fewer patient consultations per patient in the penicillin allergy test arm relative to usual care (95% CI: -0.60, 0.09). In contrast, the number of inpatient spells, outpatient episodes and A&E episodes had smaller absolute differences and wider confidence intervals around the central point estimate (Table S21).

Table S21 Summary statistics for resource use, unadjusted means

	Penicillin allergy test n=401	Usual care n=410	Mean difference (95% CI)
Primary care consultations	1.20	1.45	-0.25 (-0.60 to 0.09)
Primary care antibiotic prescriptions	1.10	1.49	-0.39 (-0.73 to -0.04)
Continuous inpatient spells	0.37	0.34	0.03 (-0.09 to 0.16)
Outpatient episodes	2.57	2.57	0 (-0.62 to 0.63)
Accident and emergency episodes	0.28	0.32	-0.04 (-0.15 to 0.08)

The costs of all primary and secondary care service use over the 12-month trial duration was £137 per patient lower in penicillin allergy test than usual care (95% CI: -583 to 320). Inpatient admissions contributed the most to the observed reduction in costs (114), followed by emergency care (13) and primary care consultations and medications (11). Estimates for all these differences were imprecise (Table S22). Higher mean QALYs were observed in the penicillin allergy test arm than Usual care.

Table S22 Summary statistics for costs (GBP) and QALYs, unadjusted means

	Penicillin allergy test(n=401)	Usual care (n=410)	Mean difference (95% CI)
Primary care	44.15	54.97	-10.82 (-24.33 to 2.69)
Inpatient	602.35	716.02	-113.67 (-431.58 to 204.23)
Outpatient	416.19	416.03	0.17 (-99.65 to 99.98)
Emergency care	68.61	81.49	-12.88 (-42.29 to 16.53)
All secondary care	1087.15	1213.54	-126.39 (-572.51 to 319.74)
All primary/secondary care	1131.30	1268.51	-137.21 (-596.83 to 322.42)
12 month QALYs	0.866	0.830	0.036 (0.012 to 0.060)

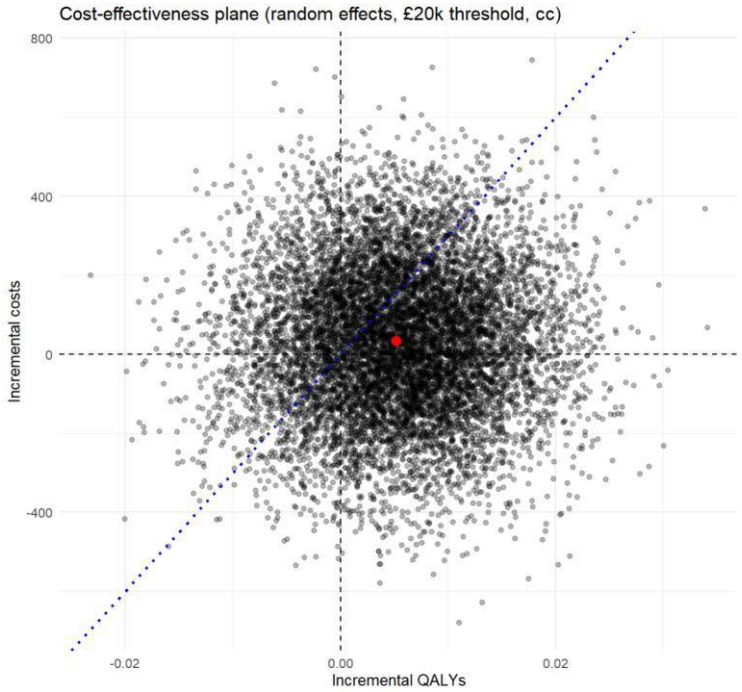
Table S23 presents summary results using incremental QALYs estimated in complete case analysis, for a range of different methods of adjusting for baseline differences. Estimates across methods are consistent with penicillin allergy test having an incremental cost per QALY gained of £6500 or lower, and a probability of cost-effectiveness of 60% or higher.

Table S23 Summary results for different adjustment methods (complete case analysis of QALYs; N=612)

	Incremental costs (GBP)	**Incremental QALYs**	**ICER (GBP/QALY)**	**At stated threshold, incremental net health benefit (*probability cost-effective, italics*)**	
				£20,000	**£30,000**
Mixed effects	33.93	0.0052	6,552	0.0035 *61.92%*	0.0040 *66.34%*
Mixed effects, time under observation	33.72	0.0076	4,436	0.0059 *68.28%*	0.0065 *72.85%*
Partitioned estimator	43.98	0.0083	5,295	0.0061 *69.83%*	0.0068 *76.02%*
Seemingly unrelated regression	4.81	0.0083	579	0.0081 *72.30%*	0.0082 *77.24%*

An illustration of the degree of uncertainty in ICER and net benefit estimates is presented in Fig S3. This figure plots individual bootstrap estimates of incremental costs of penicillin allergy test (measured against the vertical axis) and incremental QALYs (against the horizontal axis). The slope of the diagonal corresponds to the cost-effectiveness threshold of £20,000 per QALY, such that the bootstrap estimates lying above the diagonal represent studies with ICER above the cost-effectiveness threshold and bootstrap estimates below correspond to studies that have ICERs below the threshold. Therefore, the proportion of the total of bootstraps that fall below the diagonal correspond to the probability of cost-effectiveness, that is, 61·92 in Table S24.

Figure S3 Sampling uncertainty in cost effectiveness of penicillin allergy test (complete case analysis of QALYs; n=612)



The probability of penicillin allergy test being cost-effective varies with how much policy-makers are willing to pay per QALY gained (Figure S4). However such probability approaches a plateau with as willingness to pay per QALY rises and reaching a maximum value below 75%.

Figure S4 Penicillin allergy test Cost-effectiveness acceptability curve (complete case analysis of QALYs; n=612)

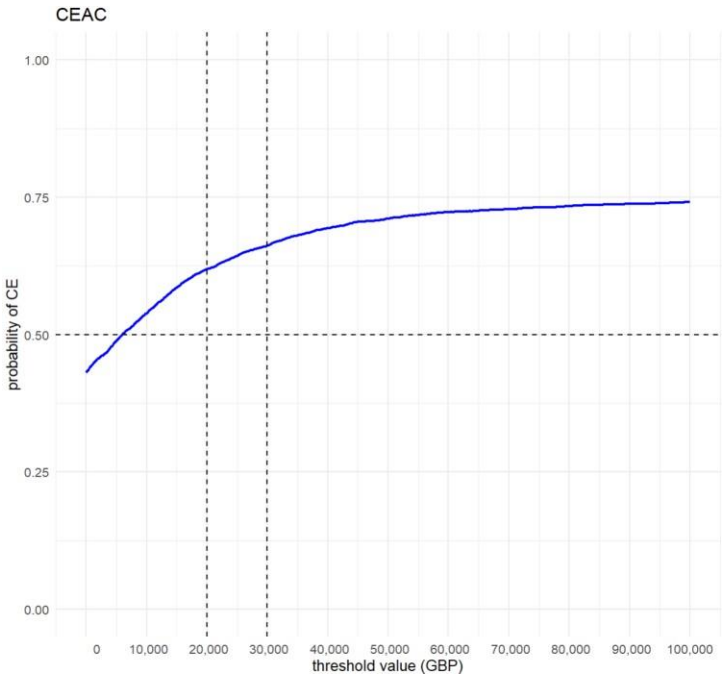


Table S24 presents summary results when multiple imputation methods are used to assign QALY values to trial participants with missing QALY data, including the full ITT sample in the analysis, for estimates derived from different methods and assumptions. The multiple imputation results display point estimates of the ICER that are of more similar magnitude across methods, and results in smaller differences in the probability of cost-effectiveness across methods, compared to the complete case analysis (Table S25).

Table S24 Summary results for different adjustment methods (imputed QALY analysis; n=811)

	Incremental costs (GBP)	Incremental QALYs	ICER (GBP/QALY)	At stated threshold, incremental net health benefit (*probability cost-effective, italics*)	
				£20,000	£30,000
Mixed effects	55.61	0.0051	10,938	0.0023 *57.85%*	0.0032 *63.92%*
Mixed effects, time under observation	55.39	0.0077	7,152	0.0049 *64.46%*	0.0059 *69.70%*
Partitioned estimator	77.97	0.0061	12,704	0.0022 *56.61%*	0.0035 *63.02%*
Seemingly unrelated regression	27.94	0.0065	4,289	0.0051 *65.00%*	0.0059 *69.26%*

Table S25 Sensitivity analyses (complete case analysis; n=612)

	Incremental costs (GBP)	Incremental QALYs	ICER (GBP/QALY)	At stated threshold, incremental net health benefit (*probability cost-effective, italics*)	
				£20,000	£30,000
As treated	223.91	0.0048	46,584	-0.0064 *29.52%*	-0.0027 *39.47%*
HES costing	237.52	0.0052	45,873	-0.0067 *29.35%*	-0.0027 *40.03%*
56 day costing	75.86	0.0052	14,651	0.0014 *53.50%*	0.0026 *57.25%*
Leeds costing	30.61	0.0052	5,911	0.0036 *62.49%*	0.0042 *67.18%*

Irrespective of the various modelling approaches taken, penicillin allergy test is found more likely than not to be cost-effective. That is, the probability of cost-effectiveness exceeds 50% at both a threshold of £20,000 or £30,000 per QALY. We conduct further sensitivity analysis, where we find two exceptions to these results in the 'As treated' analysis, when those patients who did not receive the intervention despite their having been randomly allocated to the penicillin allergy test arm are reassigned to the control group for the purpose of analysis, and the analysis that used the HES tariff for a day case allergy visit instead of the penicillin allergy test costs based on micro-costing; in these cases the probability of cost -effectiveness is 40% at the £30,000 threshold (Table S24). We present both point estimates for the incremental cost-effectiveness ratio (ICER) and incremental net health benefit (measured in net incremental QALYs per patient). In all cases, where positive, the ICER represents a ratio of positive incremental costs and positive incremental QALYs, and so can be interpreted in the usual way, with a lower ICER representing greater cost-effectiveness.

In further analysis we explored penicillin allergy test cost-effectiveness in the mixed effects model analysis across subgroups of trial participants defined by their risk of requiring antibiotic use, according to age, gender, number of QOF conditions and antibiotic medications use before enrolment into ALABAMA. penicillin allergy test was found to have the greatest likelihood of being cost-effective in female patients (86%), those with two or more antibiotic prescriptions in the previous 24 months (68%), two or more QOF conditions (64%) and aged 65 and older (61%). In contrast penicillin allergy test has a probability of cost-effectiveness of 16% in male patients (Table S26).

Table S26 Subgroup analyses (complete case analysis; n=612)

	Incremental costs (GBP)	**Incremental QALYs**	**ICER (GBP/QALY)**	**At stated threshold, incremental net health benefit (*probability cost-effective, italics*)**	
				£20,000	**£30,000**
Age <65 (*n*=416)	47.79	0.0037	13,041	0.0013 *53.66%*	0.0021 *57.02%*
Age 65+ (*n*=196)	64.59	0.0097	6,683	0.0064 *60.71%*	0.0075 *65.23%*
QOF <2 (*n*=301)	97.16	0.0022	44,181	-0.0027 *42.51%*	-0.0010 *46.23%*
QOF 2+ (*n*=311)	35.24	0.0086	4,093	0.0068 64.27%	0.0074 *67.96%*
Abx < 2 (*n*=348)	229.61	0.0052	44,036	-0.0063 *34.52%*	-0.0024 *42.88%*
Abx 2+ (*n*=264)	-129.95	0.0022	-60,371 (*dominant*)	0.0086 *67.71%*	0.0065 *66.20%*
Male (*n*=162)	176.83	-0.0163	-10,824 (*dominated*)	-0.0252 *15.94%*	-0.0222 *14.73%*
Female (*n*=450)	-25.32	0.0130	-1,961 (*dominant*)	0.0142 *85.85%*	0.0138 *90.58%*

Discussion

The within trial evaluation of penicillin allergy test found it to result in reduced costs of inpatient health care service use and primary care consultations and use of antibiotic medications, although these effects were estimated with substantial uncertainty. The uncertainty in these results led to a likelihood of penicillin allergy test cost-effectiveness to range between just above 50% to slightly above 70% in the overall ALABAMA population when exploring a range of approaches to handle features of data missingness and censoring mainly due to early trial termination.

We found some sensitivity analyses that resulted in penicillin allergy test having a less than 50% probability of cost -effective, an exception to the qualitative findings associated with other results. These occurred when we used day care HRG tariff for allergy testing to evaluate the costs of penicillin allergy test and, on separate analysis, when we adopted an 'As Treated' analysis where patients randomised to the penicillin allergy test arm who did not receive testing were re-assigned to the control group for analysis. With regard to the first of these analyses, unlike the unit costs of penicillin allergy test we estimated by micro-costing (at £234 for SPT/IDT+OC or £155 for direct OC) and used in the base case analysis, the day case HRG tariff in question (at £368) is not specific to penicillin allergy testing and does not provide information on which staff perform the tests. The 'As Treated' analysis results on the other hand are slightly surprising and suggest that, on average, patients on the penicillin allergy test arm who were not tested may have had a better prognosis than patients allocated to penicillin allergy test who did follow through with their allocated treatment as intended.
A previous observational study in the US compared the healthcare service use of Kaiser Permanente members over a 3.6 year follow up period after receiving penicillin allergy testing with matched controls and found the cases to have 0.09 fewer outpatient department visits and 0.13 fewer emergency department visits, per year (Macy et al. 2017). Our respective estimates of 0.06 and 0.04 fewer such visits corroborate the direction of the observational effects although are significantly smaller.

The amount of uncertainty resulting from the early termination of ALABAMA is reflected in the wide confidence intervals around the estimated effects on secondary care costs, the levels of probability of cost-effectiveness in our results that while pointing to exceed 50% tend to reach a maximum level below 75%.
A limitation of our analysis stems from the high proportion of trial participants (25%) with missing data on health- related quality of life outcomes and the variability of the timing in its recording, which was a result of the early termination of the study. Another limitation is that we only measured health -related quality of life data for primary events (i.e. those where an antibiotic of study interest was prescribed) in primary care, thus omitting episodes of antibiotics prescriptions in hospital. On the other hand, the use of linked hospital episode statistics data allowed us to maximise cost data capture for participants who had not completed their 12-month follow-up at the time the study was stopped. While multiple imputation of missing health-related quality of life outcomes led to small change in probability of penicillin allergy test cost-effectiveness relative to analysis based on complete cases, 62% vs. 58% respectively, these are still moderate probabilities and reflect a high degree of uncertainty that future studies may be able to address.

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Intracluster Correlation Coefficients for primary, secondary and health economics outcomes

Outcome	ICC
Primary Analysis	
Proportion of participants who received prescriptions for a penicillin (Binary)	0.04
Secondary Analyses	
Treatment response failure (Binary)	<0.0001
Duration of symptoms rated 'moderately bad' or worse (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Received a prescription for an antibiotic (Binary)	<0.0001
Number of prescriptions for antibiotics (Count)	0.03
Total number of days of all antibiotic prescriptions (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Toal DDD for all antibiotics prescriptions (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Received a prescription for a penicillin (Binary)	<0.0001
Number of prescriptions for a penicillin (Count)	<0.0001
Total number of days of prescriptions for a penicillin (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Total DDD for all prescriptions of a penicillin (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Received a prescription for non-penicillin antibiotics (Binary)	0.01
Number of prescriptions for non-penicillin antibiotics (Count)	0.02
Total number of days of prescriptions for non-penicillin antibiotics (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Total DDD for all prescriptions of non-penicillin antibiotics (Continuous – skew)	Quantile regression comparing medians – no ICC.
Admitted to hospital within 56 days of the index prescription (Binary)	0.17
Number of hospital admissions within 56 days of the index prescription (Count)	<0.0001
Length of hospital stay (days) for admissions within 56 days of the index prescription (Continuous – skew)	Quantile regression comparing medians – no ICC.
Mortality (Binary)	Unadjusted analyse – No ICC
MRSA infection/colonisation (Binary)	Fisher's exact test – No ICC
Cdiff. Infection (Binary)	Fisher's exact test – No ICC
De-labelled at 3 months post randomisation	Fisher's exact test – No ICC
De-labelled at 12 months post randomisation	Fisher's exact test – No ICC
De-labelled up to 3 months and remained de-labelled at 12 months	Fisher's exact test – No ICC
De-labelled up to 12 months and re-labelled between 3 and 12 months	Fisher's exact test – No ICC
Exploratory Analyses	
Admitted to hospital during the 12-month trial period (Binary)	<0.0001
Number of hospital admissions during the 12-month trial period (Count) Number of hospital admissions during the 12-month trial period (Count)	<0.0001
Length of hospital stay (days) for admissions during the 12-month trial period (Continuous – skew data)	Quantile regression comparing medians – no ICC.
Sensitivity analyses	
As treated population	0.05
Excluding participants who did not have complete follow-up	0.03
Excluding participants who had delayed penicillin allergy test	0.05
Subgroup Analyses	
Age (<65, ≥65 years)	0.04
Number of QOF (<2, ≥2)	0.04
IMD (<Median, ≥Median)	0.03

Site recruitment information

Site ID	*Site Name*	*Total No Recruited/Randomised*
23	Healthcare First*	52
35	Mayford House Surgery	42
8	Garforth Medical Centre	35
9	Moorfield House	35
27	Chevin Medical Practice	35
54	The Three Spires MP	35
30	The Spa Surgery (Harrogate)	34
4	Whitehall	33
31	Eastgate Medical Practice	33
49	Nethergreen Surgery	32
45	Posterngate Surgery	30
17	Orchard Croft Medical Centre	27
19	Blackburn Rd.Medical Ctr.	26
39	Chapelthorpe Medical Centre	24
43	Haworth Medical Practice (Modality)	24
15	Saltaire and Windhill MP	21
14	The Moss	20
51	Shaftesbury Medical Centre	19
18	Trinity Medical Centre (incorporating Sandal Castle Medical Centre)	17
41	Church Avenue Medical Group	17
1	Gibson Lane	15
11	Windmill HC	15

Site ID	*Site Name*	*Total No Recruited/Randomised*
29	Stockwell Road Surgery	15
58	Crosshills Medical Practice (modality)	15
48	St Martins Practice	14
6	Kippax Hall Surgery	12
26	Fisher Medical Centre (Modality)	12
20	Springbank Surgery	11
42	Ecclesfield Group Practice	11
60	Farfield Group Practice (modality)	11
5	Hillfoot Surgery	10
28	Silsden Medical Practice (Modality)	10
10	Gables Surgery	8
22	Eightlands Surgery	8
36	North House Surgery	8
38	Maybush Medical Centre	8
55	Heeley Green Surgery	8
46	Westgate Surgery	6
13	Hyde Park	5
34	Station Lane MP	5
44	Mosborough Health Centre	5
2	Craven Road	4
33	Tieve Tara MC	4
40	Haigh Hall (Affinity)	4
59	Holycroft Surgery (modality)	4
47	Kilmeny Group Medical Practice (Modality)	3
3	Fieldhead Surgery	1
7	Hillside Bridge	Never Recruited
12	Spa Surgery	Never Recruited

Site ID	*Site Name*	*Total No Recruited/Randomised*
32	Rose Medical Practice	Never Recruited
50	Shipley Medical Practice (Affinity)	Consented 3 but 0 randomised

* PCN consists of 3 practices: Pinfold Surgery, Queen Street Surgery, Park View Normanton

ALABAMA approved ethical amendments to protocol			
Substantial Amendments			
Number	Amendment to protocol	Approval date	Version # / date
1	Updated to mention that participants receive Symptom Diary reminder emails if they decide to complete their diary online.	09-May-19	v2.0 04-Feb-2019
2	Protocol not amended		
3	Protocol not amended		
4	Protocol is updated to mention: - Number of feasibility practices is changes from "8" to "at least 8". - Patients are now being offered an option of verbal consent over the phone as well as the face-to-face consent visit with their GPs/RNs. - Consent for the qualitative interviews with patients and clinicians will be obtained verbally. - Adding the mailout to non-responders to boost recruitment in each practice. - Non-responders may also be contacted by phone by practice staff or delegates to discuss their potential participations. - Patients in control arm may also now be invited to participate in a qualitative interview. - Inclusion criteria are updated to add the word "current" to the sentence "penicillin allergy record". - "Planning to become pregnant during the course of study" is now deleted from exclusion criteria. - In exclusion criteria, the sentence "Currently taking (or recently taken, within 10 days) systemic steroids" is changed to "Currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pre-testing." - This paragraph is added to the exclusion criteria: "GPs may also want to exclude vulnerable patients who are deemed to be unsuitable to participate for other reasons such as, but not limited to, terminal illness, reliability, mental illness, learning difficulties, anxiety, and other family circumstances." - "Promotion" section (7.1) is now added to the study procedure section: we will promote the study through posters in GP practices and pharmacies. Patients will also be approached opportunistically by their local GPs. - APPENDIX A: STUDY FLOW CHART has been amended with a sentence regarding the verbal consent process - Inclusion Criteria number 4 has been amended with 'Receipt of' being replaced with 'Prescribed'.	10-Jan-20	v3.0 06-Dec-2019
5	Re. qualitative study. Given the COVID-19 pandemic, the trial team would like to carry out additional interviews/or focus groups prior to the main trial to explore patients' views on attending health services during the pandemic. We would like to contact the patients who previously consented to being interviewed but did not take part in an interview for the feasibility study. These patients will be contacted by telephone by a member of the research team to invite them. Patients will be invited to participate in a telephone or online focus group or one-on-one interview. Questions will explore patients' experience of taking part in ALABAMA and thoughts on attending health care services during the COVID pandemic, willingness to use protective measures and views on ability to travel to hospital.	05-Oct-20	v4.0 14-Sep-2020

ALABAMA approved ethical amendments to protocol			
Substantial Amendments			
Number	Amendment to protocol	Approval date	Version # / date
6	Proposed change in primary outcome data collection from the method proposed in v 3.0 of the protocol (6 Dec 2019). The primary outcome remains unchanged but the method of collection will be from notes review if the symptom diary is not completed. This proposal has been made in response to low completion rates of the diary.	03-Feb-21	v5.0 20-Jan-2021
7	The main changes proposed in this amendment are: 1) Increasing the target number of sites from 70 to 140 2) Changing change the target number of participants per practice from 30 to 15-21. 3) Pre-consent text messages are updated make it clear that the consent appointments will be verbal not face-to-face. 4) Adding two new non-responder letters	28-May-21	v6.0 10-May-2021
8	Exclusion criterion 'currently receiving or due to start immunosuppressive medication' has been removed. History of dermographism has been removed from exclusion criteria. Exclusion criteria amended to allow patients that take medication with antihistamine properties, and are unable to temporarily withhold these or patients with isolated dermographism, to participate if discussed with research team prior to consent. The wording in Protocol V6.0 unnecessarily restricts certain tasks to Research Nurses, this has been updated to clarify that other trained and delegated members of the trial team may assist.	05-Jan-22	v7.0 26-Nov-2021
9	The main purpose of this amendment is to 1) Remove Average Daily Quantity (ADQ) as a secondary outcome measure for the effects of PAAP on total antibiotic prescribing, update the list of antibiotics in the inclusion criteria, add the collection of basic demographics to baseline assessments, amend the sample size to allow for a range of between 80-90% power analysis and remove the clinician questionnaire from the process evaluation 2) To create a 'Post Allergy Testing Information Sheet' to instruct patients on taking penicillin home and what they need to do if they experience a delayed reaction 3) Update the patient information sheet and pre-test intervention booklet to include the option of one singular dose for oral challenge testing for the patients deemed low risk 4) Update the patient results letter to request that the patient updates their allergy status in any health apps (if applicable) and also to change the length of time required to withhold antihistamines so that it is in line with the protocol Changes to protocol: Average Daily Quantity (ADQ) has been removed as a secondary outcome measure for the effects of PAAP on total antibiotic prescribing. Sample size amended to allow for a range of between 80-90% power analysis Updated list of antibiotics in inclusion criteria Added the collection of basic demographics to Baseline Assessments Clinician questionnaire removed from process evaluation Appendix C updated to include the option of single dose challenge depending on a risk assessment.	14-Jun-22	v8.0 10-May-2022

ALABAMA approved ethical amendments to protocol			
Substantial Amendments			
Number	Amendment to protocol	Approval date	Version # / date
10	The Alabama trial is participating as a host trial in a PrinciPIL SWAT (study withing a trial) evaluation. The PrinciPIL study is sponsored by Cardiff University and funded by the Medical Research Council (IRAS project ID 305905, REC reference 22/EE/0040), it has received the necessary regulatory and ethical approvals for the overarching SWAT intervention which will be collecting and evaluating data from multiple SWATs, run in multiple host trials (including the Alabama trial). Copies of both the HRA & HCRW approval letter and the REC favourable opinion letter dated 21st February 2022 are part of this submission. Information about the PrinciPIL SWAT study has been added as a new section to the ALABAMA Protocol. The PrinciPIL SWAT study will compare the Alabama standard patient information leaflet (ALABAMA – Patient Information Sheet) with the PrinciPIL (ALABAMA_PIS_SWAT_V1.0_Clean_ 10Jun2022). The PrinciPIL patient information leaflet was developed with extensive input on benefit and harm presentation from stakeholders (including patients, research ethics committee members, clinicians, senior trial managers). The aim of the overarching PrinciPIL SWAT study is to test whether patients exposed to PrinciPILs had fewer negative side effects. The main outputs from the study will be a report on effects of using PrinciPILs and guidelines designing them. As a host trial, the Alabama trial is seeking ethical approval to: 1. embed an evaluation of the SWAT intervention into the Alabama trial (fully anonymised patient data on reported adverse events, recruitment/retention rates and aggregated demographic data)2. securely transfer data on the effect of the SWAT intervention in the trial to the PrinciPIL SWAT evaluation lead. Additionally, we have made changes to clarify the time points of evaluation for outcome measures, clarify that randomisation will be minimised by antibiotic prescriptions in a 24-month period as per exclusion criteria, amend the exclusion criteria to make it clear that pregnancy and breastfeeding are only applicable at enrolment, and to highlight that opportunistic recruitment is encouraged. Statement added to clarify that all trial staff will be trained to work in accordance with the conditions and principles of Good Clinical Practice. Cost effectiveness section has been updated, as well as an addition to appendix G - infections that would be followed up as a primary event.	20-Sep-22	v9.0 17-Jun 2022

ALABAMA approved ethical amendments to protocol			
Substantial Amendments			
Number	Amendment to protocol	Approval date	Version # / date
11	The purpose of this amendment is to remove the requirement to preliminary screen the list of potentially eligible patients pulled from SystmOne. The current procedure for screening ALABAMA patients is that the practice, once they have been invited to join the 'ALABAMA unit' in SystmOne, run a bespoke report of potentially eligible patients. This report includes only some of the eligibility criteria (due to coding restrictions in SystmOne) and therefore it produces a 'long list' of patients, in some cases 800+ patients. The GP then has to check every single patient against the full eligibility criteria before each one can be invited to take part. This requirement was intended as a safety net to avoid inviting unsuitable patients, however, we've received feedback from sites and collaborators that this preliminary screening of the list prior to invitation is extremely time consuming and unreliable in removing all unsuitable patients. It is also raised quite regularly as a blocker for GP participation, as they do not have the capacity to screen a full list of potentially eligible patients. We are therefore removing the preliminary screening as a requirement and sending invites to all potentially eligible patients, making it clear that eligibility will need to be assessed and confirmed prior to consent. This approach means the GP, or delegated staff member, will only need to do a full eligibility check on those patients who express an interest in taking part, rather than all patients on the potentially eligible 'long' list. We believe it will significantly ease the burden on GP practices and encourage more practices to take part. Additionally, we are confident that inviting all patients to take part will improve equity and standardisation of recruitment as some GPs had been applying their own selection criteria, without our knowledge.	08-Nov-22	v10.0 03-Oct-2022

ALABAMA approved ethical amendments to protocol			
Substantial Amendments			
Number	Amendment to protocol	Approval date	Version # / date
12	The main purpose of this amendment is to change the primary outcome to 'The effects of PAAP on penicillin prescribing' from 'Effects of PAAP in improving patient health outcomes'. The sample size calculation has also been updated in response to the new primary outcome. This is in response to a meeting with the funder to discuss recruitment and timelines. Unfortunately, the ALABAMA study has been massively impacted by the aftermath of COVID in terms of primary and secondary care resource and recruitment has never reached the level required to meet the recruitment target for the original primary outcome in the current project timeframe. The funder could not provide a costed extension and therefore asked the study team to make the necessary changes to make the best use of the data collected in the timeframe left. The funder (NIHR) has been made aware of our response to change the primary outcome and is fully supportive of this decision. We have also added 1 additional secondary outcome (effect of PAAP on de-labelling) and an exploratory outcome to review safety outcomes. This is in response to discussions with the TMG who all agreed that these would be worthwhile outcomes to capture. Additional changes include amending the documentation to remove all reference to testing taking part in an immunology clinic. This is in response to opening other secondary care sites where testing is taking place in clinics that are adapted to safely complete allergy testing. We have also added the option of patients to have a 'trial partner' - someone to support them with the trial process, questions, and documentation if they feel a need for this. Furthermore, we have removed all information regarding ALABAMA taking part in the PrinciPIL study as this is no longer an option since recruitment in now coming to a close. The study has also been granted a non-cost extension until April 2024	12-Jul-23	v12.0 10-Jul-2023
13	The main purpose of this amendment is to update the cost effectiveness analysis section of the protocol in relation to the change in primary outcome and provide further information on planned analysis for differences in costs and QALYs that are likely to accrue after the end of the 12-month trial follow-up. Another exploratory outcome has been added to the protocol ‘Effects of PAAP on all outcomes for follow up past 12 month’ and clarification provided on the source of data for the primary outcome and secondary outcomes. Furthermore, in response to processing an application to NHSE (NHS digital) for the HES data, NHSE have stipulated the requirement for a privacy notice to be published on the ALABAMA website. CRN South West Peninsula have been added as a site as one GP site was green lit and recruited in this area, however, adding this area as a site has been omitted in error previously.		v13.0 05-Oct-2023
14	The main purpose of this amendment is to update the protocol to allow for all healthcare professionals to be interviewed as part of the process evaluation. The privacy notice also requires minor changes to align with the Patient Information Sheet.	04-Jan-24	v14.0 16-Nov-2023