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Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance (ALABAMA): protocol for a multicentre, parallel-arm, open label, randomised pragmatic trial

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Abstract

Objectives

Incorrect penicillin allergy records are recognised as an important barrier to the safe treatment of infection and affect an estimated 2.7 million people in England. Penicillin allergy records are associated with worse health outcomes, and antimicrobial resistance (AMR). The ALlergy AntiBiotics And Microbial resistAnce (ALABAMA) trial aims to determine if an intervention package, centred around a penicillin allergy assessment pathway (PAAP) initiated in primary care, is safe and effective in improving patient health outcomes and antibiotic prescribing.

Methods

The ALABAMA trial is a multicentre, parallel-arm, open label, randomised pragmatic trial with a nested pilot study. Adults (≥18 years) with a penicillin allergy record and who have received antibiotics in the previous 24 months will be eligible for participation. Patients will be randomised to either usual care or intervention to undergo a pre-emptive PAAP using a 1:1 allocation ratio. The primary outcome measure is the percentage of treatment response failures within 28 days of an index prescription. 2090 and 1592 participants are estimated to provide 90% and 80% power, respectively, to detect a clinically important absolute difference of 7.9% in primary outcome at one year between groups. The trial includes a mixed-methods process evaluation and cost-effectiveness evaluation.

Ethics and dissemination

Results will be presented in peer-reviewed journals and at international conferences. Research Ethic Committee (REC) approval was granted by the NRES Committee London Bridge.

The study will be conducted (using Good Clinical practice guidelines) according to the principles of the Declaration of Helsinki and in accordance with other relevant national guidelines, regulations, and acts. An independent Data Monitoring Committee (DMC) will review efficacy and safety data by treatment allocation, and a Trial Steering Committee will provide oversight of the trial.

Trial Registration

ISRCTN20579216

Article Summary

Strengths and limitations of this study

- This is the first randomised controlled trial of penicillin allergy assessment initiated in primary care patients assessing both patient health and antibiotic prescribing outcomes.
- The ALABAMA intervention package is co-designed with patient public involvement contributors, and is centred around a penicillin allergy assessment pathway (PAAP) providing support materials to encourage clinicians and patients to make desired behaviour changes. The PAAP comprises patient selection (low anaphylaxsis risk), penicillin allergy testing, and updating of electronic health records that a definitive allergy assessment was undertaken and de-labelling where appropriate. It has not been previously evaluated in a randomised controlled trial in primary care patients. The multi-centre design including patients from a number of primary care regions across England will support external validity and implementation.
- PAAP is quicker than the current 'gold standard' testing pathways. In ALABAMA, patients will be risk stratified and offered either a direct oral challenge or skin testing prior to oral challenge test. The safety of implementing PAAP has been supported by a nested pilot study, but will be confirmed in the trial.
- The trial includes a mixed-methods process evaluation which will assess how the intervention package influenced clinician and patient behaviour and delivery of care. This together with a cost-effectiveness evaluation will inform future implementation of PAAP into usual clinical care within the National Health Service.
- This trial recruitment period includes the COVID-19 pandemic and will provide an insight on the impact of the pandemic on clinical trial processes spanning primary and secondary care.

Keywords

Penicillin Allergy, Antibiotic, Clinical Trial, Antibiotic Resistance

Background

A record of penicillin allergy (PenA) in a patient's medical notes has a marked effect on antibiotic (antibacterial) prescribing, both an increase in total use and a radical change in the agents selected.[1-5] In primary care patients, the presence of a PenA record has been associated with higher rates of treatment failure, higher mortality, *Clostridioides difficile* infection, and antimicrobial resistance (AMR) in the form of meticillin resistant *Staphylococcus aureus*.[4 5]

PenA records are common and arise either because of genuine allergy symptoms during a course of treatment or, more often, because side effects and symptoms, related to the index infection requiring antibiotic treatment, are mislabelled as allergies. In the United Kingdom (UK), PenA prevalence is approximately 6%.[5] However, fewer than 1 in 10 patients with a PenA record are truly allergic after formal assessment.[6-8] Consequently, an estimated 2.7 million people in the UK are potentially prevented from accessing highly effective penicillin due to an incorrect PenA record.[5]

Macrolide, tetracycline, cephalosporin, quinolone and clindamycin prescribing are all more common in primary care patients with a record of penicillin allergy compared to those without, and antibiotic prescriptions are almost twice as frequent in patients with a PenA record.[4 5] Evidence from United States of America (USA) and elsewhere suggests that antibiotic-allergies affect health outcomes, and increase mortality, length of stay and costs. [5,8]

PenA records are also 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 2.3 million adult primary care patients found that a lack of response to treatment and MRSA were significantly more common in patients with a PenA record.[5] The 2019 WHO AWaRe Classification groups antibiotics into three stewardship categories: "Access, Watch and Reserve", and aims to promote use of Access antibiotics in order to combat AMR.[12] Patients with PenA are more likely to be prescribed antibiotics belonging to the Watch and Reserve groups which have a higher propensity to drive AMR.[13]

The gold standard test with which to establish tolerance to penicillin is a drug provocation test (which includes an oral challenge test), but current UK and European guidelines advise that patients should first be skin tested, using prick or intradermal tests, or both.[14 15] This identifies patients who are IgE-sensitised, and provides risk stratification for progression to an oral challenge test. Assessment of patients with PenA in specialist clinics is provided within the National Health Service (NHS) and is often performed over at least two clinic visits; the first, to undertake history and perform skin testing; the second to assess reactions and undertake a penicillin oral challenge test, followed by communication of results. Currently, most patients who are eligible to undergo allergy assessment are not offered the service because of a lack of testing capacity.[16] We have developed a 'Penicillin Allergy Assessment Pathway' (PAAP) which includes a 'one-stop' allergy testing process. PAAP differs from current standard UK and European guidelines in that it offers patients who have been assessed as 'low risk' of true allergy an abbreviated test consisting of direct oral challenge, i.e. with no preceding skin tests, and consistent with more recent guidelines for non-allergists[17]. The direct oral challenge approach is already used routinely for children in the UK and several studies have demonstrated safety and efficacy in adults. A recent systematic review has found that direct oral challenge testing by non-allergists is safe and reported an incidence of 1% (95% CI, 0-2%) of immediate or delayed reactions in a pooled analysis of 69 studies.[18] Patients whose histories are not clearly low risk still need to undergo skin testing, and only proceed to oral challenge if this is negative.

To enable assessment of the PAAP, clinicians and patients need to be supported to encourage referral and attendance for PAAP and if delabelled, prescribing and use of penicillin as appropriate. As such, a behavioural intervention package was developed to include the PAAP and support materials for clinicians and patients. The development of the intervention is reported elsewhere.[19]

The **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resistance (ALABAMA) trial (full title: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance) is aimed at determining whether an intervention package, centred around a PAAP, is safe and effective in improving patient health outcomes and antibiotic prescribing. The trial protocol is described below.

Methods

Study design

ALABAMA is a multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested pilot study and embedded process evaluation and cost-effectiveness evaluation. The protocol for ALABAMA was developed according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines.[20] A nested pilot was conducted from December 2018 to July 2020 to determine the safety, feasibility, acceptability, and practicality of the ALABAMA trial. This included a 'stop/go' assessment criteria which was based on feasibility, recruitment, and safety.

The study is registered with the International Standard Randomised Controlled Trial Number (ISRCTN20579216). Enrolment started at the first general practice (GP) site as part of the feasibility study in October 2019 and recruitment is expected to finalise in 2023.

Participants and Eligibility

Between 1592 and 2090 participants will be recruited from participating NHS general practices in England. The inclusion and exclusion criteria are described in Table 1. Potential participants who meet the eligibility criteria 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 The Phoenix Partnership (TPP), healthcare technology company, and made available for running locally on SystmOne (an electronic health record system used in primary care that was developed by TPP), thus participating general practices must be using SystmOne. Potentially eligible patients will then be sent an invitation letter.

Patients interested in taking part will return an expression of interest form to the trial team. They will then be telephoned and booked into an either face to face or telephone appointment with their GP or delegated member of staff at a time that is convenient to them. During this appointment, their GP or a delegated member of staff, will confirm their eligibility and obtain their consent to participate in the trial. Participants must meet the inclusion criteria and have none of the exclusion criteria.

Patient and Public Involvement

Antimicrobial resistance (AMR) and antimicrobial allergy lack patient groups/hospital networks/local charities to draw upon for PPIE, necessitating us building a bespoke ALABAMA PPIE-Allergy Forum(PPIE-AF) to contribute to the research design, execution and dissemination strategy. The PPIE-AF comprises people with previous penicillin allergies, including those that has been overturned and can now receive penicillins. It also includes those with self-reported (unsubstantiated) penicillin allergy.

All of our research adopts a co-design approach where our PPIE-AF contributors input to ensure we designed a trial that is patient-centered with the shared goal to maximise improved NHS care and patient outcomes. Specifically, the trial was designed to be inclusive and to minimise long/multiple hospital visits during the penicillin allergy testing. This is therefore the first trial designed as a 'one stop' efficient allergy assessment for low risk individuals. The guidance to participants about de-labelling also facilitates ease of future NHS implementation and patient uptake of penicillin allergy testing.

PPIE-AF members have been engaged in both the nested pilot and main trial - they reviewed and provided input into the protocol development for the ethics submission. They contributed to the design of the qualitative enquiry and ethics submission, bringing their lived experience to shape the interview topic guide. They guided the need to develop educational material to support patients if their penicillin allergy status is changed.

PPIE-AF members have ensured that our inclusion criteria is broad and includes patient groups that are high antimicrobial users. The research team incorporated their views that limiting eligibility to a single group of patients (e.g. only those with COPD) would limit the applicability of findings and thus potential benefit in patients across health conditions and age groups, especially those over 65 years, who probably have the highest rate of inappropriate penicillin allergy labels and who may benefit from testing. PPIE-AF members have ensured the trial material is understandable and appropriate for patients considering participation and that the trial intervention itself is not too onerous and has a clear patient-centred approach. The PPIE-AF have great ambitions for dissemination using a proven Theatre of Debate involvement to make our research findings accessible to all based on our similar award winning application in NIHR COVID and Me.

Table 1: Inclusion and exclusion Criteria

Inclusion	Exclusion
• 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 in the previous 24 months N.B.1 Patients with a penicillin allergy record and a recent penicillin prescription would still be eligible because their allergy status will need assessment and records correcting if necessary. N.B.2 Patients who have been formally tested for penicillin allergy in the past and been found not to be penicillin allergic but still has a medical record indicating a penicillin allergy, are eligible for the trial.	• Life expectancy estimated <1 year by GP • Unable to attend immunology clinic • 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 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, 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 take part but will need to be discussed with the research team prior to consent.

SystmOne and ALABAMA Unit

GP's recruiting into ALABAMA will have the electronic health record system, SystmOne (The phoenix Partnership (TPP), Leeds, UK), set up as part of their routine practice. TPP, the healthcare technology company that has developed SystmOne, has 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. The 'ALABAMA unit' is equivalent to setting up a new practice within SystmOne to which GPs can refer patients and allowing approved users to access patient electronic medical 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.

The 'ALABAMA unit' allows the GP practice to pull a bespoke report of potentially eligible patients, allows the research team to track the de-labelling process of patients confirmed as negative and enables the follow up of ALABAMA patients given an antibiotic in the 12-month period following randomisation.

Randomisation

Randomisation will be performed using Sortition (an online randomisation system developed by the Primary Care Clinical Trials Unit of University of Oxford). Participants will be randomised to either usual care or the intervention arm using an allocation ratio of 1:1. Allocation will be minimised by general practice, age, number of antibiotic prescriptions in the 24 months (12 months for participants recruited to nested pilot) prior to randomisation, and number of QOF registered diseases to ensure balance of allocation of these baseline covariates. Both the participants and the recruiter will know which arm they have been randomised into.

The trial statistician will remain blinded to treatment allocation when performing the final analysis.

Data Recording and Record Keeping

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

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.

Trial Outcomes

Primary outcome

The primary objective is to determine whether the intervention package is clinically effective in improving patient health outcomes. This will be measured using 'treatment response failure' rate which is 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 over at least one year subsequent to randomisation. These predefined infections are ones managed in the community for which a penicillin would be recommended as first line therapy (See Appendix A). Assignment of antibiotic prescriptions as primary events will be checked by clinical members of the research team blinded to both the trial allocation and outcome of the event.

Secondary outcomes

Secondary outcomes include:

1. Effects of PAAP duration on symptoms rated 'moderately bad' or worse by patients after antibiotic treatment
2. Effects of PAAP on antibiotic use (total duration, number of courses, defined daily doses (DDD), and an equivalent analysis by antibiotics class e.g. penicillins)
3. Effects of PAAP on number of hospital admissions and length of hospital stays
4. Effects of PAAP on mortality rates
5. Effects of PAAP on number of patients with Meticillin-resistant *Staphylococcus aureus* (MRSA)infection/colonisation.
6. Effects of PAAP on number of patients with *Clostridioides difficile* infection.
7. Cost effectiveness for the PAAP intervention compared to usual care through self-reported health-related quality of life (HRQoL) outcomes

The process evaluation will explore patient and clinician views and experiences of the PAAP, trial procedures and implications on de-labelling on subsequent antibiotic prescribing and penicillin use through interviews. We will measure the influences on patient behaviour change through questionnaires.

Trial Procedures

Participant screening, eligibility checks, and consent will be carried out by GPs or appropriately trained authorised staff delegated to do this on behalf of the GP. Subsequent trial procedures are carried out by the ALABAMA trial team, who will communicate PAT results to GPs.

Study Intervention Package

The intervention package includes the PAAP and support materials for clinicians and patients[19].

On entry to the study, practices will receive site training and support materials for clinicians to help them in discussing and referring patients to the PAAP. Clinicians will receive an information leaflet (titled *Penicillin Allergy Testing: Information for general practice*) that includes evidence-based information to increase knowledge about penicillin allergy testing and

motivation to refer patients for a penicillin allergy test (PAT) and prescribe penicillin after a negative PAT result. They will also receive training in making changes to the electronic health record when a patient receives a negative allergy test result.

The central component of the study intervention package is the penicillin allergy test (PAT) which will be carried out in three stages:

- Stage-1: in primary care – Clinical History.
- Stage-2: Skin testing in hospital clinic (this may not be needed for all participants, see Figure 1)
- Stage- 3: Oral Challenge Test in hospital clinic/at home.

Stage 2, if needed, and stage 3 are performed together during half-a-day clinic visit which, if there is no initial reaction, the oral challenge test will continue to complete 3 days oral antibiotics. Figure 1 shows the PAT flow.

All participants in the intervention arm will be posted a pre-test intervention leaflet (titled Penicillin Allergy Testing: going for a test') prior to their PAT appointment to inform them about incorrect allergy records, how they may benefit from having a PAT and what the test involves.

On completion of PAT, practices will be informed of the test result and instructed to update the participant's electronic health records accordingly. Entry of the PAT result codes into the patient electronic health record activates additional behaviour change materials: pop ups that appear when a GP prescribes antibiotics for a trial participant to remind them of a change to PenA records, if appropriate. (Figure 2)

Participants will receive an allergy test result letter. If they have tested negative, they will receive a second booklet (titled Penicillin Allergy Testing: a negative test result) and an Intervention Card. The booklet informs patients about the reliability of the test results and consequences of a negative test result. The intervention card is a laminated credit card-sized card that says which test the patient has had and confirms the negative allergy result.

The study comparator is usual care with subsequent monitoring for antibiotic prescriptions and follow-up for trial outcomes as determined by the clinical indication for antibiotics. Usual care in this context, means antibiotics prescribed by their general practitioner according to routine clinical practice.

Symptom diary and Questionnaires

- Symptom diary - Participants will be asked to complete a symptom diary when they receive an antibiotic for a pre-defined list of infections in the 12-month period from randomisation. Information collected will include the predominant presenting symptoms, symptom severity, 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. Participant diaries will either be recorded on paper CRFs or directly in to the REDCap database.

- Patient allergy belief questionnaire - Participants will be asked to complete this at baseline and if applicable 28 – 30 days after completing the PAAP.

- EQ-5D-5L questionnaire [21]- Participants will be asked to complete this at baseline, 12 months after randomisation and, if applicable, 28 – 30 days after any GP appointment where an antibiotic was prescribed for one of the pre-defined infections.

Linkage with NHS Digital

The SystmOne ALABAMA unit will remain in existence for 10 years after the close of the trial to support an evaluation of long term outcomes. Participants will have their electronic health record interrogated via linkage with NHS digital for data on hospital admissions (HES data), details of antibiotic prescriptions during their admission (GP notes review and secondary care notes review) and mortality data (ONS data). Participants will be consented for this as part of the current ALABAMA trial consent process.

Safety

PenA testing is routinely carried out in the NHS and is known to carry a very small risk of anaphylaxis and death. To minimise this risk for participants undergoing the pre-emptive PAT,

any patient with a prior history suggestive of anaphylaxis or a previous serious reaction to penicillin will be excluded.

Telephone calls by the trial team at 4 – 6 days and 28 – 30 days after PAAP will collect information on adverse events (AEs) and serious adverse events (SAEs) associated with PAAP.

AEs and SAEs occurring up to 28 days after an antibiotic prescription from their general practitioner for any pre-defined infections will be captured through the participant diary and telephone calls by the research team 2 – 4 days and 28 – 30 days after the start of an antibiotic prescription. We will capture any AEs that result in a change of antibiotic prescription through the safety review telephone calls and/or notes review.

All SAEs identified during the ALABAMA trial will be assessed for their relatedness to PAAP or antibiotic prescriptions for any of the pre-defined infections. Anaphylaxis to an antibiotic will be considered an SAE as part of the ALABAMA trial.

Participants in the nested pilot study were 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 notes review, HES and mortality data, at month 12.

Mixed-methods process evaluation

The mixed-methods process evaluation will include a patient questionnaire (see questionnaires, and semi-structured telephone interviews with patients and clinicians). Patients will be asked to complete an allergy belief questionnaire at baseline and, if applicable, 28 – 30 days after the PAAP.

Purposive sampling will be used to identify a subset of clinicians who will be invited to take part in an interview at the end of the trial to discuss their experiences.

A subset of patient participants will be interviewed once they have completed the PAAP and received their allergy test result to understand their experiences and also for those patients who have received subsequent antibiotic prescriptions following de-labelling; this will include those delabelled but refusing penicillin. Patients and clinicians invited to take part in telephone interviews will be provided with patient information sheets (PISs) and Informed Consent Forms (ICFs) specific to the qualitative component of the process evaluation.

Statistical Analysis

Sample size calculation

A total sample size of 2090 or 1592 participants (1045 or 791 per trial arm respectively) will provide 90% or 80% power, respectively to detect a clinically important absolute difference of 7.9% in re-prescription rate (used as surrogate for treatment response failure) at one year between groups at 5% level of significance (2-sided). We plan to recruit 2090 but will fall back on 1592 if recruitment is challenging, as recruitment has commenced during the COVID-19 pandemic and will continue in the post pandemic climate. The sample size has been adjusted assuming only 50% of participants will require at least one prescription within 1 year from randomisation and allowing for 10% dropout. The first 96 participants of the total will comprise the sample for the nested pilot study.

Primary and secondary outcomes

An intention-to-treat (ITT) analysis will be conducted for the primary outcome and will include all randomised patients irrespective of what treatment they actually receive. Analysis for the primary outcome, i.e. "treatment response failure", will be analysed using a generalised linear mixed effects model specifying a Binomial distribution with a log link function. GP site will be included in the model as a random effect while relevant baseline covariates and other minimisation factors will be treated as fixed effects. A similar approach will be used for other binary secondary outcomes, while continuous outcomes will be analysed using linear mixed effects models. Appropriate regression models (such as Poisson regression, Hurdle models etc.) will be used for the analysis of count outcomes.

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. 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.

Mixed methods process evaluation analysis

Descriptive statistics (frequencies and percentages) will be used to summarise responses to questionnaire data.

Data from interviews with clinicians and patients, will be analysed using thematic analysis taking an inductive approach [22 23]. 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.

Cost effectiveness analysis

A within-trial economic evaluation will estimate the effect on quality of life, costs and incremental cost per quality-adjusted life year (QALY) gained for PAAP versus usual care from the perspective of the NHS and Personal Social Services. The analysis will use trial data collected to 12 months follow up post randomisation.

Costs for delivering the PAAP intervention will be measured as part of the trial and the costs of delivering usual care will be calculated based on resource use collected in the trial and unit costs from the published literature. Primary and secondary health care service use will be estimated, respectively, from SystOne electronic records and the linked individual participant Hospital Episode Statistics Health Resource Group (HRG) data. Prescribing data in secondary care will be obtained by the trial team through hand searching of patient records in lead centre and other centres when possible or by accessing electronic prescribing systems, if available. Health care service costs will be estimated by valuing primary or community care service use using unit costs from published sources [24], use of medications with list prices from the BNF and HRG unit costs from NHS Reference Costs. QALYs will be calculated using area under the curve interpolations between baseline and 12 month EQ-5D-5L utility data collected in the trial and linked ONS mortality data over the first year after randomisation. No discounting will be applied to costs and QALYs and incremental costs per QALY gained as the time horizon will be limited to 12 months.

Costs will be analysed using generalised linear models with a gamma family and log link [25 26] to account for skewness, and adjust for general practice, age, number of antibiotic prescriptions

in the 12 months prior to randomisation, and number of QOF registered diseases, as well as baseline EQ5D5L score [27]. A similar approach will be applied to analyse QALYs, based on parametric survival models and predicted utility differences between trial arms.

Missing data will be imputed using established methods [28]. Results will be presented in terms of incremental cost per QALY gained and cost per treatment failure avoided at 12 months. Sampling uncertainty will be analysed using the bootstrap method [29] and joint uncertainty in costs and QALYs will be analysed using cost-effectiveness acceptability curves [30]. Sensitivity analyses will explore variations in key cost and QALY assumptions, including interpolation of utility scores from baseline to 12 month data collection points, dis-utilities associated with adverse events, and joint parametric distributions used to model costs and QALYs.

Ethics and Dissemination

This trial is in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice. Research Ethic Committee (REC) approval was granted by the NRES Committee London Bridge. The trial is registered with the ISRCTN registry (ISRCTN20579216).

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

The primary trial results will be submitted for publication to an international, peer-reviewed journal, regardless of the nature of the results. Authorship will be determined by the chief investigators 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. Patient and public dissemination is also planned.

Conclusion

The importance of antibiotic resistance (AMR) and the need to reduce its impact is well recognised.[31] Penicillins are the most commonly prescribed antibiotics[32] and remain first-line therapy for many common infections. However, allergy to penicillin is commonly reported by patients and the presence of a PenA record in a patient's notes leads to the avoidance of recommended first line penicillin antibiotics and the use of alternative non-penicillin antibiotics which can be less effective, have more side effects and have a greater propensity to drive AMR.

Evidence shows that approximately 5% of patients who have a PenA record are found to have genuine allergy after non specialist allergy assessment.[33] This trial aims to address the large discrepancy between reported and true allergy rates and will determine if introducing 'pre-emptive' testing for patients who are more likely to receive antibiotics in the future, could impact upon antibiotic prescribing, yield patient benefits, limit AMR/Healthcare associated infection (HCAI) and deliver NHS cost savings.

The novel design of the PAAP allows direct oral challenge testing of patient participants deemed to have low risk of a genuine allergic reaction and is intended to make the penicillin allergy testing more efficient. If PAAP is found to be acceptable to patients, this streamlined approach to penicillin allergy testing would enable more patients to be tested within current resources. Additionally, PAAP need not be confined to take place in an immunology clinic and could be undertaken by appropriately trained staff, such as pharmacist, in all units with facilities to deal with severe allergic reactions.

The PAAP is supported by a behavioural package, providing support materials to clinicians and patients to encourage referral to and attendance at PAAP and prescription and use of penicillin following de-labelling, where appropriate. These materials were developed with input from stakeholders including patient public involvement contributors to ensure they address clinician and patients' needs.

Other strengths of the ALABAMA study include the nested pilot study which ensured the safety of PAAP before transition to the main trial and the multi-centre design which allows recruitment of patients from a number of primary care regions across the United Kingdom, thus reinforcing the external validity of the trial. In addition, the mixed-methods process evaluation will allow us to understand how the intervention package was used by clinicians and patients, help to interpret the trial findings and provide insight into optimal implementation. As a result, positive findings from the ALABAMA trial will be readily implementable in the NHS.

This trial has developed unique trial processes utilising SystmOne for data collection which will be discussed elsewhere, however this novel technology can potentially be used to improve trial processes for future primary care research.

The ALABAMA trial is being conducted amidst the COVID-19 pandemic and therefore will provide an insight into the effect of the pandemic on trial processes, in particular on participant recruitment and on how safety procedures for participants and trial staff are implemented.

This trial is the largest randomised trial aiming to pre-emptively address incorrect penicillin allergy records and has potential to significantly impact care by improving patient health outcomes, improving antibiotic prescribing, reducing antimicrobial resistance and overall reducing NHS costs.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

JS and SP are the co-chief investigators and had the original idea for this study, developed the protocol, and obtained the funding. JS and SP led the development of the research question, study design along with KA, SA, JC, JB, EM, CCB, KC, MD, PH, CEP, RS and SS manage the trial and coordinate the operational delivery of the study protocol. UG, RW, and LMY contribute and provide the statistical plan. RMM provided health economics input. MS, STC and MW provided the qualitative section. All authors provided critical review and final approval of manuscript.

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Trial Status

Enrolment started at the first general practice (GP) site as part of the feasibility study in October 2019. The current protocol is version 10.0 03-OCT-2022

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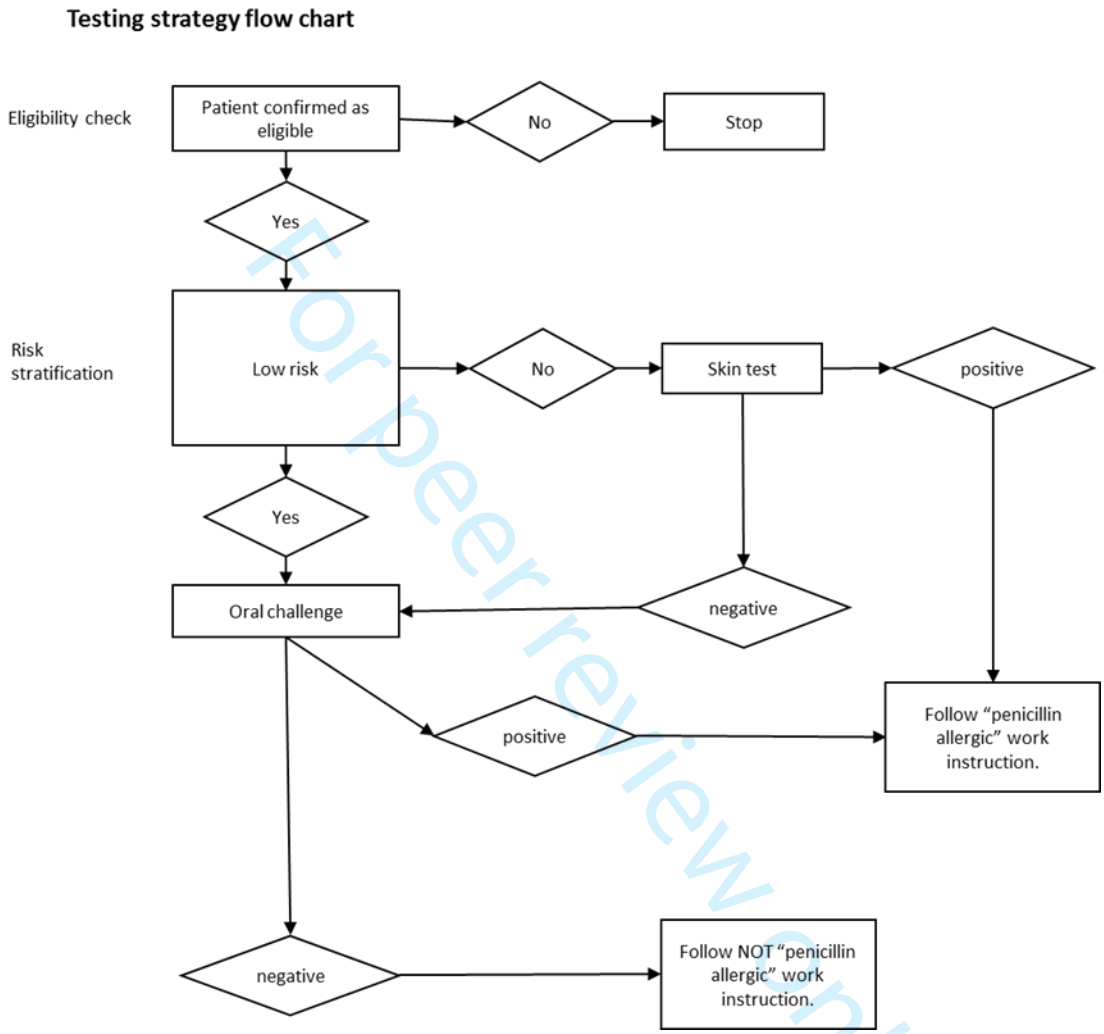
Figure 1. The ALlergy AntiBiotics And Microbial resistance (ALABAMA) trial penicillin allergy testing (PAT) strategy.

Figure 2. outlines the ALABAMA Flow Diagram for Penicillin Allergy Assessment Pathway (PAAP)

Figure 1. The **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resistance (ALABAMA) trial penicillin allergy testing (PAT) strategy



ALABAMA Flow Diagram

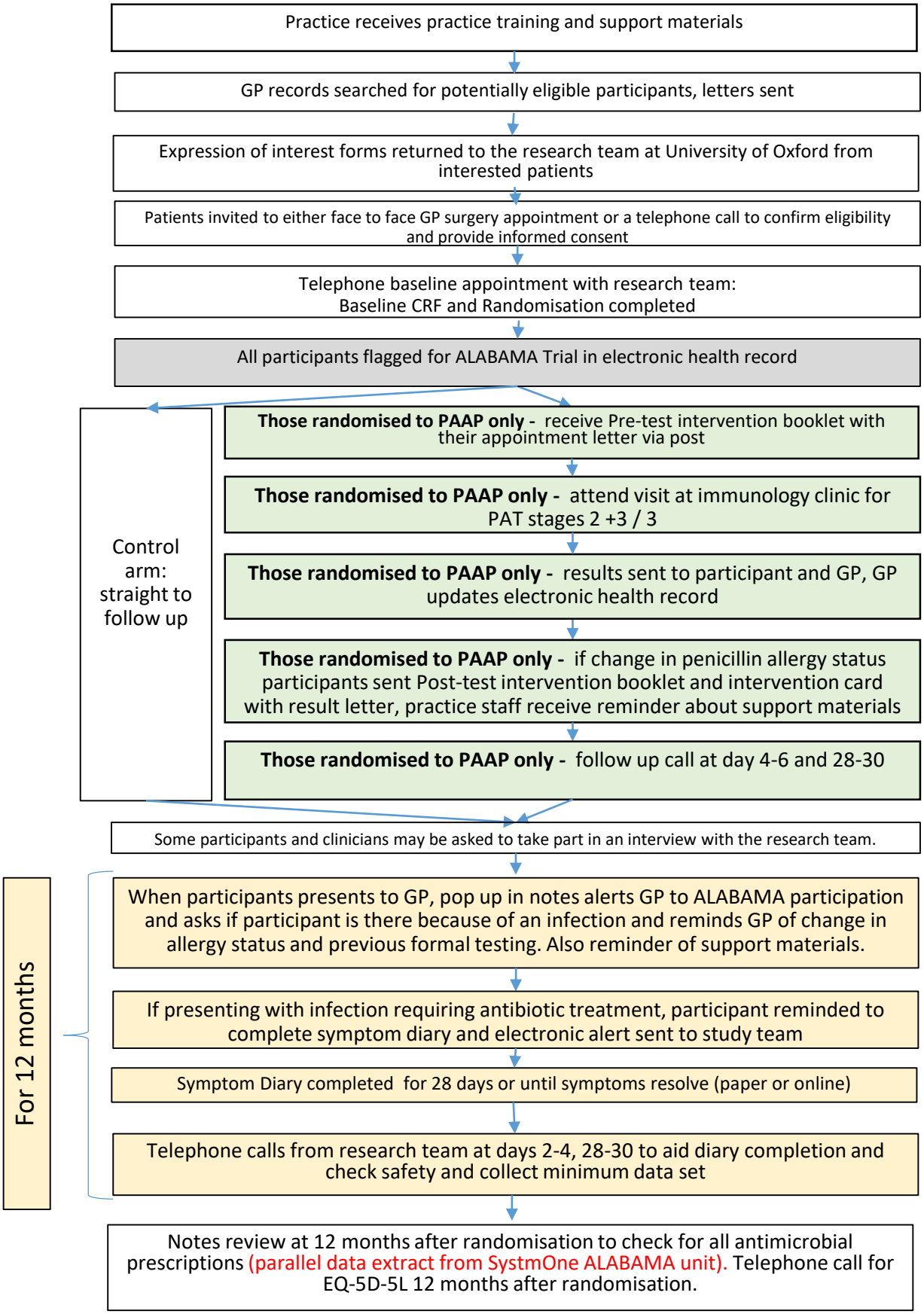


Figure 2 outlines the ALABAMA Flow Diagram for Penicillin Allergy Assessment Pathway (PAAP)

APPENDIX A: 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

BMJ Open

Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance (ALABAMA): protocol for a multicentre, parallel-arm, open label, randomised pragmatic trial

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	Research, School of Medicine
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Immunology (including allergy), Infectious diseases
Keywords:	IMMUNOLOGY, INFECTIOUS DISEASES, PRIMARY CARE, Clinical Trial

Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance (ALABAMA): protocol for a multicentre, parallel-arm, open label, randomised pragmatic trial

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Abstract

Introduction

Incorrect penicillin allergy records are recognised as an important barrier to the safe treatment of infection and affect an estimated 2.7 million people in England. Penicillin allergy records are associated with worse health outcomes, and antimicrobial resistance (AMR). The ALlergy AntiBiotics And Microbial resistAnce (ALABAMA) trial aims to determine if an intervention package, centred around a penicillin allergy assessment pathway (PAAP) initiated in primary care, is safe and effective in improving patient health outcomes and antibiotic prescribing.

Methods and analysis

The ALABAMA trial is a multicentre, parallel-arm, open label, randomised pragmatic trial with a nested pilot study. Adults (≥18 years) with a penicillin allergy record and who have received antibiotics in the previous 24 months will be eligible for participation. Between 1592 and 2090 participants will be recruited from participating NHS general practices in England. Participants will be randomised to either usual care or intervention to undergo a pre-emptive PAAP using a 1:1 allocation ratio. The primary outcome measure is the percentage of treatment response failures within 28 days of an index prescription. 2090 and 1592 participants are estimated to provide 90% and 80% power, respectively, to detect a clinically important absolute difference of 7.9% in primary outcome at one year between groups. The trial includes a mixed-methods process evaluation and cost-effectiveness evaluation.

Ethics and dissemination

This trial has been approved by London Bridge Research Ethics Committee (Ref: 19/LO/0176). It will be conducted in compliance with Good Clinical Practice guidelines according to the Declaration of Helsinki. Informed consent will be obtained from all subjects involved in the study. The primary trial results will be submitted for publication to an international, peer-reviewed journal.

Trial registration

ISRCTN20579216.

Article summary

Strengths and limitations of this study

- This study is a randomised controlled trial of penicillin allergy assessment initiated in primary care assessing patient health outcomes.
- The multi-centre design recruiting patients from more than 50 primary care sites from across England will support external validity and NHS implementation.
- Penicillin allergy assessment pathway (PAAP) offers efficient, and economical, one-step testing over current 'gold standard' testing pathways.
- ALABAMA is a complex intervention with an integrated mixed-methods process evaluation to guide future NHS implementation.
- By necessity, the trial is open label and de-labelling of participants in the intervention arm may influence clinician behaviour across all participants.

Keywords

Penicillin Allergy, Randomized Clinical Trial, Antibiotic Resistance, Antimicrobial Stewardship.

Introduction

A record of penicillin allergy (PEN allergy) in a patient's health record has a marked effect on antibiotic prescribing, both an increase in total use and a radical change in the agents selected. [1-5] In primary care patients, the presence of a PEN allergy record has been associated with higher rates of treatment failure, higher mortality, *Clostridioides difficile* infection, and antimicrobial resistance (AMR) in the form of methicillin resistant (also known as meticillin-resistant) *Staphylococcus aureus*. [4-5] PEN allergy records are common and arise either because of genuine allergy symptoms during a course of treatment or, more often, because side effects and symptoms related to the index infection are mislabelled as allergies. In the United Kingdom (UK), PEN allergy prevalence is approximately 6%. [5] However, fewer than 1 in 10 patients with a PEN allergy record are truly allergic after formal assessment. [6-8]

Consequently, an estimated 2.7 million people in the UK are potentially prevented from accessing highly effective penicillin due to an incorrect PEN allergy record. [5]

Macrolide, tetracycline, cephalosporin, quinolone and clindamycin prescribing are all more common in primary care patients with a record of penicillin allergy compared to those without, and antibiotic prescriptions are almost twice as frequent in patients with a PEN allergy record. [4-5] Evidence from United States of America (USA) and elsewhere suggests that antibiotic-allergies affect health outcomes, and increase mortality, length of stay and costs. [5,8] PEN allergy records are also 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 methicillin-resistant *Staphylococcus aureus* (MRSA). [9-11] Preliminary investigations of 2.3 million adult primary care patients found that a lack of response to treatment and MRSA were significantly more common in patients with a PEN allergy record. [5] The 2019 WHO AWaRe classification groups antibiotics into three stewardship categories: "Access, Watch and Reserve", and aims to promote use of Access antibiotics in order to combat AMR. [12] Patients with PEN allergy are more likely to be prescribed antibiotics belonging to the Watch and Reserve groups which have a higher propensity to drive AMR. [13]

The gold standard test with which to establish tolerance to penicillins is a drug provocation test (which includes oral challenge testing), but previous UK and US guidelines advised that patients should first be skin tested, using prick or intradermal tests, or both. [14-15] The latest US guidelines now recommends for "low risk" historical penicillin allergy patients, direct oral challenge without preceding skin testing. [16] This identifies patients who are IgE-sensitised, and provides risk stratification for progression to an oral challenge test. Assessment of patients with PEN allergy in specialist clinics is provided within the National Health Service (NHS) and is often performed over at least two clinic visits; the first, to undertake history and perform skin testing; the second to assess reactions and undertake a penicillin oral challenge test, followed by communication of results. Currently, most patients who are eligible to undergo allergy assessment are not offered the service because of a lack of testing capacity. [17] One-stop allergy testing offers the potential to improve allergy testing capacity. This currently differs from UK standard and European guidelines in that it offers patients who have been assessed as 'low risk' of true allergy an abbreviated test consisting of direct oral challenge, i.e. with no preceding skin tests, and consistent with more recent guidelines for non-allergists. [18] The direct oral challenge approach is already used routinely for children in the UK and several studies have demonstrated safety and efficacy in adults. A recent systematic review has found

that direct oral challenge testing by non-allergists is safe and reported an incidence of 1% (95% CI, 0-2%) of immediate or delayed reactions in a pooled analysis of 69 studies. [19] Patients whose histories are not clearly low risk still need to undergo skin testing, and only proceed to oral challenge if this is negative.

The **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resistance (ALABAMA) trial (full title: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance) will evaluate participants randomised to either usual care or to receive 'Penicillin Allergy Assessment Pathway' (PAAP). PAAP is a complex intervention, incorporating one-stop allergy testing and appropriate de-labelling of electronic health records. It will evaluate if PAAP is safe and effective in improving patient health outcomes, influencing antibiotic prescribing, and supporting healthcare implementation. ALABAMA is the first RCT to our knowledge that looks at adult penicillin allergy testing and de-labelling with a primary health outcome.

Methods and analysis

Study design

ALABAMA is a multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested pilot study and embedded process evaluation and cost-effectiveness evaluation. The protocol for ALABAMA was developed according to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines. [20] A nested pilot was conducted from December 2018 to July 2020 to determine the safety, feasibility, acceptability, and practicality of the ALABAMA trial. This included a 'stop/go' assessment criteria which was based on feasibility, recruitment, and safety.

The main ALABAMA trial evaluates a complex intervention, designed according to the MRC guidelines. [21] The complex intervention is collectively referred to as the 'Penicillin Allergy Assessment Pathway' (PAAP). This comprises: 1) an efficient direct referral for a 'one-stop' single appointment for an allergy assessment and testing; 2) appropriate guidance for clinicians to refer patients for PEN allergy testing and instruction on how to de-label, i.e. update allergy status in participants' electronic health records appropriately; 3) information for participants to encourage attendance for testing and information pre-testing to distinguish

side effects (e.g. diarrhoea) from true allergic reactions. The development of the physician and participant behavioural intervention component is reported elsewhere. [22]

The study is registered with the International Standard Randomised Controlled Trial Number (ISRCTN20579216). Enrolment started at the first general practice (GP) site as part of the feasibility study in October 2019 and recruitment is expected to finalise in 2023.

Participants and eligibility

Between 1592 and 2090 participants will be recruited from participating NHS general practices in England. The inclusion and exclusion criteria are described in Table 1. Potential participants who meet the eligibility criteria will be identified during a search of electronic health records at their general practice. The electronic search criteria have been developed centrally by the research team in partnership with The Phoenix Partnership (TPP), healthcare technology company, and made available for running locally on SystmOne (an electronic health record system used in primary care that was developed by TPP), thus participating general practices must be using SystmOne. Potentially eligible patients will then be sent an invitation letter.

Patients interested in taking part will return an expression of interest form to the trial team by post, phone or email, or by following a link to add their details to an online secure database. They will then be telephoned and booked into an either face to face or telephone appointment with their GP, or delegated member of staff, at a time that is convenient to them. The GP, and delegates, will have received full protocol training and the GP will take on the role of Principal Investigator at site. The GP, or a delegated member of staff, will confirm the patient's eligibility and obtain their consent to participate in the trial (See Appendix 1 & 2). Participants must meet the inclusion criteria and have none of the exclusion criteria.

Patient and public involvement

Antimicrobial resistance (AMR) and antimicrobial allergy lack patient groups/hospital networks/local charities to draw upon for PPIE, necessitating us building a specific ALABAMA PPIE-Allergy Forum (PPIE-AF) to contribute to the research design, execution and dissemination strategy. The PPIE-AF comprises people with previous penicillin allergies, including those that has been overturned and can now receive penicillins. It also includes those with self-reported (unsubstantiated) penicillin allergy.

Our research adopts a co-design approach where our PPIE-AF contributors input to ensure we designed a trial that is patient-centred with the shared goal to maximise improved NHS care and patient outcomes. Specifically, the trial was designed to be inclusive and to minimise long/multiple hospital visits during the penicillin allergy testing. This is therefore the first trial designed as a 'one stop' efficient allergy assessment for low risk individuals. The guidance to participants about de-labelling also facilitates ease of future NHS implementation and patient uptake of penicillin allergy testing.

PPIE-AF members have been engaged in both the nested pilot and main trial - they reviewed and provided input into the protocol development for the ethics submission. They contributed to the design of the qualitative enquiry and ethics submission, bringing their lived experience to shape the interview topic guide. They guided the need to develop educational material to support patients if their PEN allergy status is changed.

PPIE-AF members have ensured that our inclusion criteria is broad and includes patient groups that are high antimicrobial users. The research team incorporated their views that limiting eligibility to a single group of patients (e.g. only those with chronic obstructive pulmonary disease (COPD) would limit the applicability of findings and thus potential benefit in patients across health conditions and age groups, especially those over 65 years, who probably have the highest rate of inappropriate PEN allergy labels and who may benefit from testing. PPIE-AF members have ensured the trial material is understandable and appropriate for patients considering participation and that the trial intervention itself is not too onerous and has a clear patient-centred approach. The PPIE-AF have great ambitions for dissemination using a proven Theatre of Debate involvement to make our research findings accessible to all based on our similar award winning application in NIHR COVID and Me.

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
• Patient is willing and able to give informed consent for participation in the trial • Male or Female, aged 18 years or above	• Life expectancy estimated <1 year by GP • Unable to attend immunology clinic • Unsuitable for entry into testing pathway because: ▪ Allergy history consistent with anaphylaxis to penicillin

• Current penicillin allergy (or sensitivity) record of any kind in their electronic health record • Prescribed systemic antibiotics in the previous 24 months Note 1, patients with a penicillin allergy record and a recent penicillin prescription would still be eligible because their allergy status will need assessment and records correcting if necessary. Note 2, patients who have been formally tested for penicillin allergy in the past and been found not to be penicillin allergic but still has a medical record indicating a penicillin allergy, are eligible for the trial.	▪ 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 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, other family circumstances. Note 3, Patients that are currently taking medicines with antihistamine properties that cannot be temporarily withheld, or patients with isolated dermographism, may still be eligible to take part but will need to be discussed with the research team prior to consent.

SystmOne and ALABAMA unit

SystmOne is one of the major electronic health records systems used in primary care in the UK, it was developed by The Phoenix Partnership (TPP), Leeds, UK, a health technology company. Enrolment of General Practices (GPs) into the ALABAMA trial requires that they use SystmOne as their health record system. A functionality of SystmOne allows the participating GPs to share health records of consented participants, and direct referrals for allergy testing, this sharing functionality is referred to as the 'ALABAMA unit'. Delegated members of the ALABAMA trial team can gain access to the ALABAMA unit and can then view consented participants' medical records and monitor antibiotic prescribing activity by running bespoke reports within the ALABAMA unit. Participants' electronic health records will not be altered by the trial team but selected information, alerts, GP tasks and bespoke data reports can be generated, facilitating trial data capture. For example, the ALABAMA unit allows the GP practice to run a bespoke report of potentially eligible patients, allows the research team to track the de-labelling process of ALABAMA participants confirmed as PEN allergy negative, and enables the follow up of participants given an antibiotic in the 12-month period following randomisation.

Randomisation

Randomisation will be performed using Sortition (an online randomisation system developed by the Primary Care Clinical Trials Unit of University of Oxford). Participants will be randomised to either usual care or the intervention arm using an allocation ratio of 1:1. Allocation will be minimised by general practice, age, number of antibiotic prescriptions in the 24 months (12 months for participants recruited to nested pilot) prior to randomisation, and number of Quality and Outcomes Framework (QOF) registered diseases to ensure balance of allocation of these baseline covariates. Both the participants and the recruiter will know which arm they have been randomised into. The trial statistician will remain blinded to treatment allocation when performing the final analysis.

Data recording and record keeping

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.

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 2018, which requires data to be anonymised as soon as it is practical to do so.

Trial outcomes

Primary outcome

The primary objective is to determine whether the intervention package is clinically effective in improving patient health outcomes. This will be measured using 'treatment response failure' rate which is 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 over at least one year subsequent to randomisation. These predefined infections are ones managed in the community for which a penicillin would be recommended as first line therapy (See Appendix A). Assignment of antibiotic prescriptions as primary events will be checked by clinical members of the research team blinded to both the trial allocation and outcome of the event.

Secondary outcomes

Secondary outcomes are:

1. Effects of PAAP duration on symptoms rated 'moderately bad' or worse by patients after antibiotic treatment
2. Effects of PAAP on antibiotic use (total duration, number of courses, defined daily doses (DDD), and an equivalent analysis by antibiotics class e.g. penicillins)
3. Effects of PAAP on number of hospital admissions and length of hospital stays
4. Effects of PAAP on mortality rates
5. Effects of PAAP on number of patients with Methicillin-resistant *Staphylococcus aureus* (MRSA)infection/colonisation.
6. Effects of PAAP on number of patients with *Clostridioides difficile* infection.
7. Cost effectiveness for the PAAP intervention compared to usual care through self-reported health-related quality of life (HRQoL) outcomes

The process evaluation will explore patient and clinician views and experiences of the PAAP, trial procedures and implications on de-labelling on subsequent antibiotic prescribing and penicillin use through interviews. We will measure the influences on patient behaviour change through questionnaires.

Trial procedures

Participant screening, eligibility checks, and consent will be carried out by GPs or appropriately trained authorised staff delegated to do this on behalf of the GP. Subsequent trial procedures are carried out by the ALABAMA trial team, who will communicate PAT results to GPs.

Study intervention package

The intervention package includes the PAAP and support materials for clinicians and participants. [22]

On entry to the study, practices will receive site training and support materials for clinicians to help them in discussing and referring participants to the PAAP. Clinicians will receive an information leaflet (titled *Penicillin Allergy Testing: Information for general practice*) that includes evidence-based information to increase knowledge about penicillin allergy testing and motivation to refer participants for a penicillin allergy test (PAT) and prescribe penicillin after

a negative PAT result. They will also receive training in making changes to the electronic health record when a participant receives a negative allergy test result.

The central component of the study intervention package is the penicillin allergy test (PAT) which will be carried out in three stages:

- Stage-1: in primary care – Clinical History.
- Stage-2: Skin testing in hospital clinic (this may not be needed for all participants, (See Figure 1 and Appendix 3)
- Stage- 3: Oral Challenge Test in hospital clinic/followed by subsequent doses at home. (See Appendix 4)

Stage 2, if needed, and stage 3 are performed together during half-a-day clinic visit. If there is no initial reaction in clinic, the participant will continue the oral challenge test by completing 3 days oral antibiotics at home. Figure 1 shows the PAT flow.

All participants in the intervention arm will be posted a pre-test intervention leaflet (titled Penicillin Allergy Testing: going for a test') prior to their PAT appointment to inform them about incorrect allergy records, how they may benefit from having a PAT and what the test involves.

On completion of PAT, practices will be informed of the test result and instructed to update the participant's electronic health records accordingly. Entry of the PAT result codes into the participant's electronic health record activates additional behaviour change materials: pop ups that appear when a GP prescribes antibiotics for a trial participant to remind them of a change to PEN allergy records, if appropriate. (Figure 2)

Participants will receive an allergy test result letter. If they have tested negative, they will receive a second booklet (titled *Penicillin Allergy Testing: a negative test result*) and an Intervention Card. The booklet informs participants about the reliability of the test results and consequences of a negative test result. The intervention card is a laminated credit card-sized card that says which test the participant has had and confirms the negative allergy result.

The study comparator is usual care with subsequent monitoring for antibiotic prescriptions and follow-up for trial outcomes as determined by the clinical indication for antibiotics. Usual care in this context, means antibiotics prescribed by their general practitioner according to routine clinical practice.

Symptom diary and questionnaires

- Symptom diary - Participants will be asked to complete a symptom diary when they receive an antibiotic for a pre-defined list of infections in the 12-month period from randomisation. Information collected will include the predominant presenting symptoms, symptom severity, antibiotic consumption and any side effects. The diary will be completed for 28 days or until the participant's symptoms are a 'slight problem' or less (scoring 2 and below) and they have stopped their course of antibiotics. Participant diaries will either be recorded on paper CRFs or directly into the REDCap database.

- Patient allergy belief questionnaire - participants will be asked to complete this at baseline and if applicable 28 – 30 days after completing the PAAP.

- EQ-5D-5L questionnaire [23] participants will be asked to complete this at baseline, 12 months after randomisation and, if applicable, 28 – 30 days after any GP appointment where an antibiotic was prescribed for one of the pre-defined infections.

Linkage with NHS Digital

The SystmOne ALABAMA unit will remain in existence for 10 years after the close of the trial to support an evaluation of long term outcomes. Participants will have their electronic health record interrogated via linkage with NHS Digital for data on hospital admissions (HES data), details of antibiotic prescriptions during their admission (GP notes review and secondary care notes review) and mortality data (ONS data). Participants will be consented for this as part of the current ALABAMA trial consent process.

Safety

PEN allergy testing is routinely carried out in the NHS and is known to carry a very small risk of anaphylaxis and death. To minimise this risk for participants undergoing the pre-emptive

PAT, any participant with a prior history suggestive of anaphylaxis or a previous serious reaction to penicillin will be excluded.

Telephone calls by the trial team at 4 – 6 days and 28 – 30 days after PAT will collect information on adverse events (AEs) and serious adverse events (SAEs) associated with PAAP.

AEs and SAEs occurring up to 28 days after an antibiotic prescription from their general practitioner for any pre-defined infections will be captured through the participant diary and telephone calls by the research team 2 – 4 days and 28 – 30 days after the start of an antibiotic prescription. We will capture any AEs that result in a change of antibiotic prescription through the safety review telephone calls and/or notes review.

All SAEs identified during the ALABAMA trial will be assessed for their relatedness to PAAP or antibiotic prescriptions for any of the pre-defined infections. Anaphylaxis to an antibiotic will be considered an SAE as part of the ALABAMA trial.

Participants in the nested pilot study were 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 notes review, HES and mortality data, at month 12.

Mixed-methods process evaluation

The mixed-methods process evaluation will include a patient questionnaire (see questionnaires, and semi-structured telephone interviews with patients and clinicians). Participants will be asked to complete an allergy belief questionnaire at baseline and, if applicable, 28 – 30 days after the PAAP.

Purposive sampling will be used to identify a subset of clinicians who will be invited to take part in an interview at the end of the trial to discuss their experiences.

A subset of patient participants will be interviewed once they have completed the PAAP and received their allergy test result to understand their experiences and also for those participants who have received subsequent antibiotic prescriptions following de-labelling; this will include those de-labelled but refusing penicillin. Participants and clinicians invited to take part in telephone interviews will be provided with patient information sheets (PISs) and Informed Consent Forms (ICFs) specific to the qualitative component of the process evaluation.

Statistical analysis

Sample size calculation

A total sample size of 2090 or 1592 participants (1045 or 791 per trial arm respectively) will provide 90% or 80% power, respectively to detect a clinically important absolute difference of 7.9% in re-prescription rate (used as surrogate for treatment response failure) at one year between groups at 5% level of significance (2-sided). We plan to recruit 2090 but will fall back on 1592 if recruitment is challenging, as recruitment has commenced during the COVID-19 pandemic and will continue in the post-pandemic climate. The sample size has been adjusted assuming only 50% of participants will require at least one prescription within 1 year from randomisation and allowing for 10% dropout. The first 96 participants of the total will comprise the sample for the nested pilot study.

Primary and secondary outcomes

An intention-to-treat (ITT) analysis will be conducted for the primary outcome and will include all randomised participants irrespective of what treatment they actually receive. Analysis for the primary outcome, i.e. "treatment response failure", will be analysed using a generalised linear mixed effects model specifying a Binomial distribution with a log link function. GP site will be included in the model as a random effect while relevant baseline covariates and other minimisation factors will be treated as fixed effects. A similar approach will be used for other binary secondary outcomes, while continuous outcomes will be analysed using linear mixed effects models. Appropriate regression models (such as Poisson regression, Hurdle models etc.) will be used for the analysis of count outcomes.

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. 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.

Mixed methods process evaluation analysis

Descriptive statistics (frequencies and percentages) will be used to summarise responses to questionnaire data.

Data from interviews with clinicians and participants, will be analysed using thematic analysis taking an inductive approach [24,25]. 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. To further make sense of the data, we will draw in our analysis on behaviour changes theories to facilitate implementation planning.

Cost effectiveness analysis

A within-trial economic evaluation will estimate the effect on quality of life, costs and incremental cost per quality-adjusted life year (QALY) gained for PAAP versus usual care from the perspective of the NHS and Personal Social Services. The analysis will use trial data collected up to 12 months follow up post randomisation.

Costs for delivering the PAAP intervention will be measured as part of the trial and the costs of delivering usual care will be calculated based on resource use collected in the trial and unit costs from the published literature. Primary and secondary health care service use will be estimated, respectively, from SystmOne electronic records and the linked individual participant Hospital Episode Statistics Health Resource Group (HRG) data. Prescribing data in secondary care will be obtained by the trial team through hand searching of participants' health records in the lead secondary care centre and other centres when possible or by accessing electronic prescribing systems, if available. Health care service costs will be estimated by valuing primary or community care service use using unit costs from published sources [26], use of medications with list prices from the BNF and HRG unit costs from NHS Reference Costs. QALYs will be calculated using area under the curve interpolations between baseline and 12 month EQ-5D-5L utility data collected in the trial and linked ONS mortality data over the first year after randomisation. No discounting will be applied to costs and QALYs and incremental costs per QALY gained as the time horizon will be limited to 12 months.

Costs will be analysed using generalised linear models with a gamma family and log link [27,28] to account for skewness, and adjust for general practice, age, number of antibiotic prescriptions in the 12 months prior to randomisation, and number of QOF registered diseases,

as well as baseline EQ5D5L score. [29] A similar approach will be applied to analyse QALYs, based on parametric survival models and predicted utility differences between trial arms.

Missing data will be imputed using established methods. [30] Results will be presented in terms of incremental cost per QALY gained and cost per treatment failure avoided at 12 months. Sampling uncertainty will be analysed using the bootstrap method [31] and joint uncertainty in costs and QALYs will be analysed using cost-effectiveness acceptability curves. [32] Sensitivity analyses will explore variations in key cost and QALY assumptions, including interpolation of utility scores from baseline to 12 month data collection points, dis-utilities associated with adverse events, and joint parametric distributions used to model costs and QALYs.

Ethics and dissemination

This trial is in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice. Research Ethic Committee (REC) approval was granted by the NRES Committee London Bridge (Ref: 19/LO/0176). The trial is registered with the ISRCTN registry (ISRCTN20579216). The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Informed consent will be obtained from all subjects involved in study.

An independent Data Monitoring Committee (DMC) will review efficacy and safety data by treatment allocation, and a Trial Steering Committee will provide oversight of the trial.

The primary trial results will be submitted for publication to an international, peer-reviewed journal, regardless of the nature of the results. Authorship will be determined by the chief investigators 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. Patient and public dissemination is also planned. The data that support the findings of this study will be available upon reasonable request.

Discussion

The importance of antibiotic resistance (AMR) and the need to reduce its impact is well recognised. [31] Penicillins are the most commonly prescribed antibiotics [33] and remain first-line therapy for many common infections. However, allergy to penicillin is commonly reported by patients and the presence of a PEN allergy record in a patient's health record leads to the avoidance of recommended first line penicillin antibiotics and the use of alternative non-penicillin antibiotics which can be less effective, have more side effects and have a greater propensity to drive AMR.

Evidence shows that approximately 5% of patients who have a PEN allergy record are found to have genuine allergy after non specialist allergy assessment. [19] This trial aims to address the large discrepancy between reported and true allergy rates and will determine if introducing 'pre-emptive' testing for patients who are more likely to receive antibiotics in the future, could impact upon antibiotic prescribing, yield patient benefits, limit AMR/Healthcare associated infection (HCAI) and deliver NHS cost savings.

The novel design of the PAAP allows direct oral challenge testing of patient participants deemed to have low risk of a genuine allergic reaction and is intended to make the penicillin allergy testing more efficient. If PAAP is found to be acceptable to patients, this streamlined approach to penicillin allergy testing would enable more patients to be tested within current resources. Additionally, PAAP need not be confined to take place in an immunology clinic and could be undertaken by appropriately trained staff, such as pharmacists, in all units with facilities to deal with any potential severe allergic reaction.

The PAAP Is supported by a behavioural package, providing support materials to clinicians and participants to encourage referral to and attendance at PAAP and prescription and use of penicillin following de-labelling, where appropriate. These materials were developed with input from stakeholders including PPIE-AF patient public involvement contributors to ensure they address clinician and participants' needs.

Other strengths of the ALABAMA study include the nested pilot study which ensured the safety of PAAP before transition to the main trial and the multi-centre design which allows recruitment of patients from a number of primary care regions across the United Kingdom, thus reinforcing the external validity of the trial. In addition, the mixed-methods process evaluation will allow us to understand how the intervention package was used by clinicians and

participants, help to interpret the trial findings and provide insight into optimal implementation. As a result, positive findings from the ALABAMA trial will be readily implementable in the NHS.

This trial has developed unique trial processes utilising SystmOne for data collection which will be discussed elsewhere, however this novel technology can potentially be used to improve trial processes for future primary care research.

The ALABAMA trial is being conducted amidst the COVID-19 pandemic and therefore will provide an insight into the effect of the pandemic on trial processes, in particular on participant recruitment and on how safety procedures for participants and trial staff are implemented.

This trial is the largest randomised trial aiming to pre-emptively address incorrect penicillin allergy records and has potential to significantly impact care by improving patient health outcomes, improving antibiotic prescribing, reducing antimicrobial resistance and overall reducing NHS costs.

A potential limitation is that the trial recruitment period includes the COVID-19 pandemic, which may have influenced antibiotic prescribing rates.

The process evaluation will review de-labelling procedures with GPs. As the trial is open label de-labelling of participants in the intervention arm may influence clinician behaviour across all participants; it will be prudent to monitor this impact. Baseline rates of penicillin prescribing practice of those with a PEN allergy are not formally captured in the trial participating sites, although we do know the National average (4%). This will warrant further local audits within SystmOne and/or closer working with NHS-England that are now monitoring this behaviour in some geographic areas of relevance to the trial.

Trial status

Enrolment started at the first general practice (GP) site as part of the feasibility study in October 2019. The current protocol is version 10.0 03-OCT-2022.

Declarations

Competing interests

The authors declare that they have no competing interests.

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Contributors

Conceptualization, J.A.T.S., S.P., C.B., S.S., E.B., P.H. and S.T.-C.; methodology, J.A.T.S., S.P., J.B., S.A., K.A., C.E.P., M.D., J.C., E.B., P.H., R.S., R.M.-M. and K.C.; formal analysis, U.G., R.W., L.M.-Y., S.T.-C., M.W., and M.S.; investigation, S.S., S.A., R.S., M.W., and M.S.; resources, J.A.T.S., S.P., C.B., S.S., E.B. and S.T.-C.; data curation, U.G., L.M.-Y., S.T.-C., M.W., M.S., and R.M.-M.; writing—original draft preparation, K.A., C.E.P., and M.D.; writing—review and editing, All; supervision, E.B., J.C., J.A.T.S., and S.P.; project administration, C.E.P., K.A., M.D., and K.C.; funding acquisition, J.A.T.S., C.B., P.H., S.T.-C., B.S., and S.P. All authors have read and agreed to the published version of the manuscript.

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FIGURE TITLES

Figure 1. The ALlergy AntiBiotics And Microbial resistance (ALABAMA) trial penicillin allergy testing (PAT) strategy

Figure 2. ALABAMA flow diagram for penicillin allergy assessment pathway (PAAP)

APPENDIX FILES

Appendix 1. ALABAMA verbal consent form

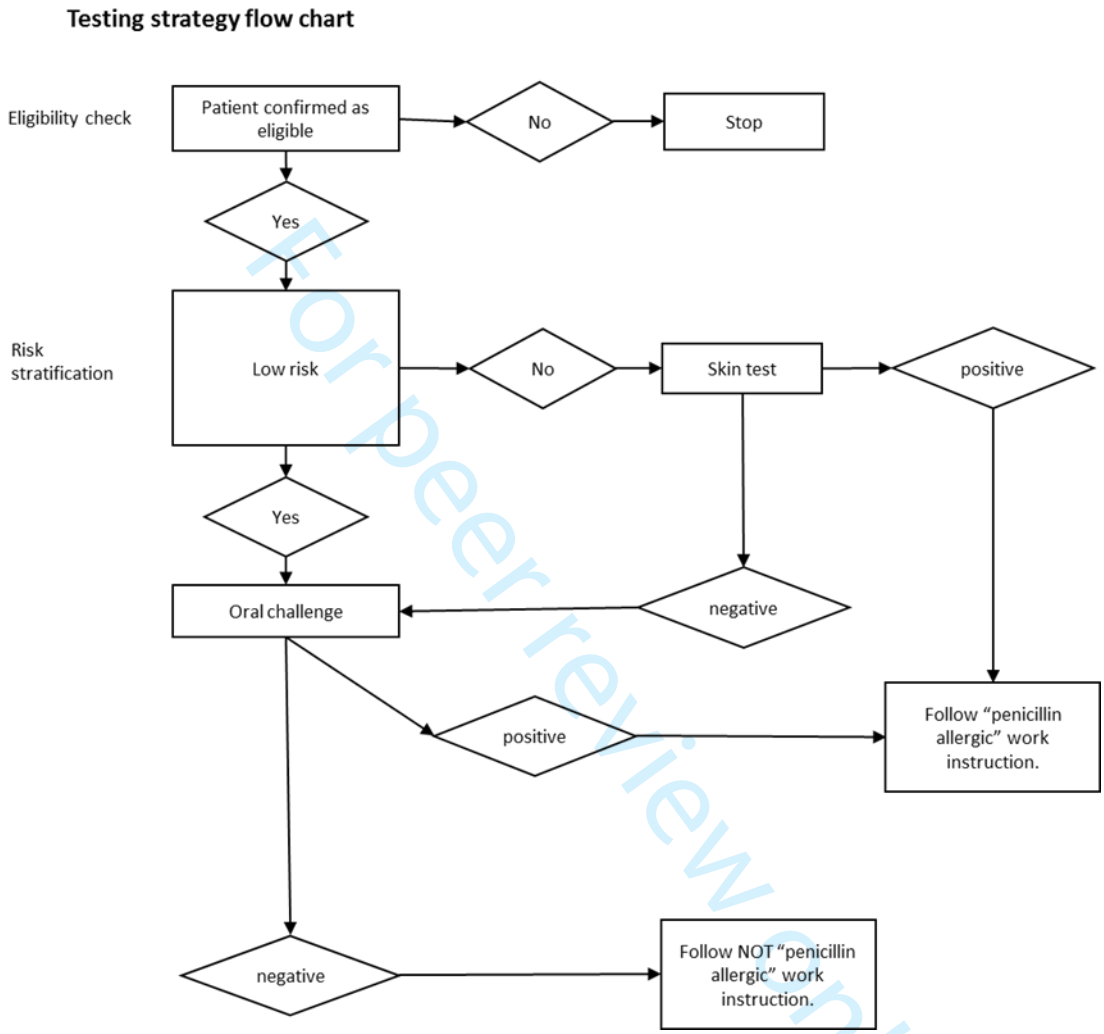
Appendix 2. ALABAMA face-to-face consent form

Appendix A. ALABAMA infections for which an antibiotic prescription would be considered a primary event and subsequently assessed for primary trial outcome

Appendix 3. Skin prick and intradermal allergy test SOP

Appendix 4. Oral challenge test SOP

Figure 1. The **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resistance (ALABAMA) trial penicillin allergy testing (PAT) strategy



ALABAMA Flow Diagram

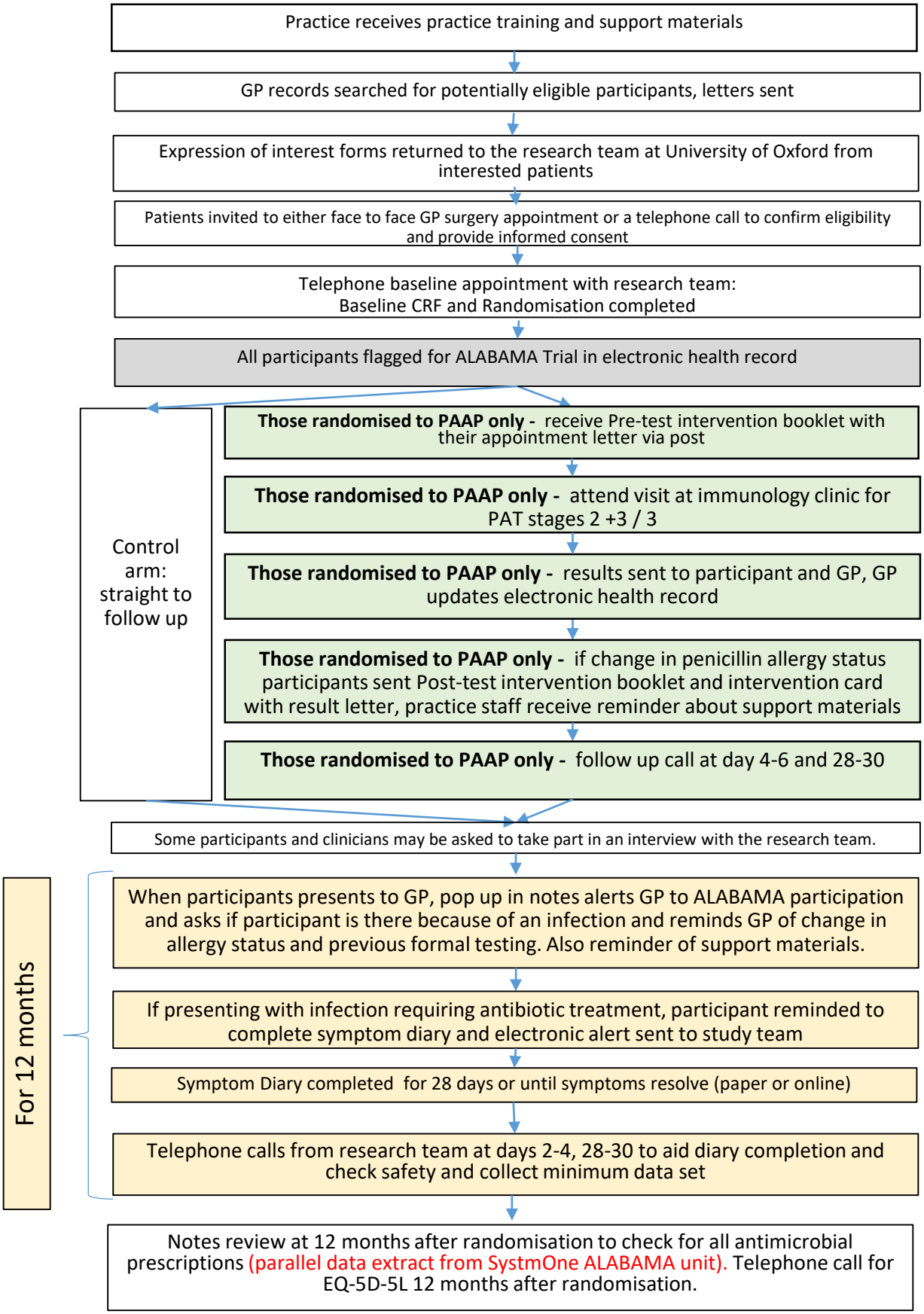


Figure 2 outlines the ALABAMA Flow Diagram for Penicillin Allergy Assessment Pathway (PAAP)

APPENDIX A: 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

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

ALABAMA ALlergy AntiBiotics And Microbial resistAnce

The Leeds Teaching Hospitals NHS NHS Trust

UNIVERSITY OF LEEDS

ALABAMA Trial Verbal CONSENT FORM

Trial Title:	**ALlergy AntiBiotics And Microbial resistAnce (ALABAMA)**: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance.
Participant ID:	**GP Practice Name:**
REC No: **19/LO/0176**	**Patient's name, Date of birth and GP surgery name confirmed?** **Tick** ☐

Investigators: Dr Jonathan Sandoe, Prof Sue Pavitt

*Write **Yes** if confirmed*

1 Do you confirm that you have read and understood the ALABAMA Information Sheet version number _____ dated: __ __ / __ __ __ / __ __ __ __ and you have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily. ☐

2 Do you understand your participation is voluntary and that you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected and that you understand that data collected up to your time of withdrawal may still be used? ☐

3 Do you understand that you will be randomised to either usual clinical care, or penicillin-allergy assessment pathway (PAAP)? You will be told which trial group you are in. ☐

4 Do you understand if you are in the PAAP group you will attend an additional appointment at the immunology clinic, Do you understand this appointment will involve skin testing (ST) and /or taking syrup solution containing penicillin called oral challenge test (OCT). ☐

5 Do you understand that if your PAAP result shows no penicillin allergy, your medical records will be updated and for future infections that require antibiotic treatment you may be prescribed a penicillin based antibiotic. ☐

6 Do you understand that you will be required to provide information to the research team through electronic, paper and telephone questionnaires? Do you consent to the ALABAMA research team to access, transfer and store this paper and electronic data. ☐

7 Do you consent to being contacted by the research team for the purposes of trial follow up and you understand that this will require you to provide the research team with your name and contact details. Do you agree to the transfer and storage of this data for use in the ALABAMA trial? ☐

8 Do you understand that your medical records, including information about general medical history, penicillin allergy history, visits to hospital, other NHS resource use and antimicrobial prescriptions will be reviewed and data collected by the ALABAMA research team for ten years after trial has ended. Do you permit these individuals to have access to your electronic health records and paper health records and any records held by NHS Digital? ☐

9 Do you understand that your name, date of birth and NHS Number will be shared with NHS Digital to enable them to supply the trial team with additional data about you for ten years after trial has ended? This may include Hospital Episode Statistics data and Mortality data. The data supplied by NHS Digital is linked by the trial team to the data collected during your participation in the ALABAMA trial. You are free to withdraw your consent for data linkage with NHS Digital at any time and it will not affect your ongoing care. ☐

10 Do you give permission for your data collected for the trial and up to 10 years after the trial has ended, to be looked at by authorised individuals from the University of Leeds, University of Oxford, authorised collaborators within the ALABAMA Trial and regulatory authorities for research purposes? Do you understand that all information collected will be used for medical research only and that you will not be identified in any way in the analysis and reporting of the results? ☐

11 Do you consent to your GP being informed of your participation within the trial and the results of the PAAP testing (if applicable)? ☐

12 Do you give permission for secondary use of your data for further research studies after the end of the trial? ☐

13 Do you agree to take part in the ALABAMA trial? ☐

14 **OPTIONAL:** Do you agree to potentially be contacted to take part in a telephone interview to discuss your experience of taking part in the ALABAMA trial? ☐

_____ _____ _____

Name of Person Taking Consent (Print) Date Signature

_____ _____

Name of Participant (Print) Date

No signature obtained from the participant as verbal consent taken by telephone.

NUFFIELD DEPARTMENT OF PRIMARY CARE HEALTH SCIENCES

ALABAMA ALlergy AntiBiotics And Microbial resistAnce

The Leeds Teaching Hospitals NHS Trust

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ALABAMA Trial ADULT CONSENT FORM

Trial Title: **ALlergy AntiBiotics And Microbial resistAnce (ALABAMA)**: Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance.

Participant ID: | | | | | | | REC Number: 19/LO/0176

Chief Investigators: Dr Jonathan Sandoe, Prof Sue Pavitt

		PLEASE INITIAL
1.	I confirm I have read and understood the ALABAMA Participant Information Sheet version number _____ dated:__ __ / __ __ __ / __ __ __ __. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
2.	I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that data collected up to my time of withdrawal may still be used.	
3.	I understand that I will be randomised to either usual clinical care, or penicillin-allergy assessment pathway (PAAP). I will be told which trial group I am in.	
4.	If I am in the PAAP group I will attend an additional appointment at the immunology clinic, I understand this appointment will involve skin testing (ST) and /or taking syrup solution containing penicillin called oral challenge test (OCT).	
5.	I understand that if my PAAP result shows no penicillin allergy, my medical records will be updated and for future infections that require antibiotic treatment I may be prescribed a penicillin based antibiotic by my GP.	
6.	I understand that I will be required to provide information to the research team through electronic, paper and telephone questionnaires. I consent to the ALABAMA research team to access, transfer and store this paper and electronic data.	
7.	I consent to being contacted by the research team for the purposes of trial follow up and I understand that this will require me to provide the research team with my name and contact details. I agree to the transfer and storage of this data for use in the ALABAMA trial.	
8.	I understand that my medical records, including information about general medical history, penicillin allergy history, visits to hospital, other NHS resource use and antimicrobial prescriptions will be reviewed and data collected by the ALABAMA research team for ten years after trial has ended. I permit these individuals to have access to my electronic health records and paper health records and any records held by NHS Digital.	
9.	I understand that my name, date of birth and NHS Number will be shared with NHS Digital to enable them to supply the trial team with additional data about me for ten years after trial has ended. This may include Hospital Episode Statistics data and Mortality data. The data supplied by NHS Digital is linked by the trial team to the data collected during my participation in the ALABAMA trial. I am free to withdraw my consent for data linkage with NHS Digital at any time and it will not affect my ongoing care.	
10.	I give permission for my data collected for the trial and up to 10 years after the trial has ended, to be looked at by authorised individuals from the University of Leeds, University of Oxford, authorised collaborators within the ALABAMA Trial and regulatory authorities for research purposes. I understand that all information collected will be used for medical research only and that I will not be identified in any way in the analysis and reporting of the results.	
11.	I consent to my GP being informed of my participation within the trial and the results of the PAAP testing (if applicable).	
12.	I give permission for secondary use of my data for further research studies after the end of the trial.	
13.	I agree to take part in the ALABAMA trial.	
14.	**OPTIONAL:** I agree to potentially be contacted to take part in a telephone interview to discuss my experience of taking part in the ALABAMA trial.	

Name of Person Taking Consent (Print)	Date	Signature

Name of Participant (Print)	Date	Signature

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3. Appendix 3: ALABAMA SOP, Skin Prick and Intradermal Allergy Test

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

Contributor	Name	Date	Signed
Written by:	Robert White Research Nurse	01.10.20	
Updated by:	Shadia Ahmed Research Fellow	10.05.22	
Approved by:	Dr. Sinisa Savic Consultant Immunologist	10.05.22	

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NHS Trust

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

Standard Operating Procedure

Skin Prick and Intradermal Testing

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

Skin prick (SPT) and intradermal (IDT) testing (SPT) are methods used to determine the presenceof 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.

4. EXCLUSIONS:

SPT and IDT reactions are inhibited by antihistamines and may be inhibited by tricyclic antidepressants, tetracyclic antidepressants, topical corticosteroids and UV light treatment. Wherepossible 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 withoral challenge

testing if they do not need SPT.

5. CAUTIONS:

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

6. 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.*

7. PREPARATION:

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

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

8. PROCEDURE:

STP and IDT

1. Ensure the patient is in a comfortable sitting position or, if needle phobic, lying down. Restarm 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.

9. 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 rubthe 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 layerof 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.

10.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 sitewith forefinger and thumb.
5. With the syringe almost against the patient's skin, insert the needle into the skin at an angleof 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.

11.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.

12.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 ≥ 3mmcompared to the initial bleb or negative control is considered a positive result.

13.COMPLICATIONS:

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

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

14.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 orsevere pruritus.

15. Appendix 3.1: 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:…… Date:…19 Aug 2019…… Approved by:…. …… Date:……02 Sep 2019……

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16. Appendix 3.2: Dilution instructions

Amoxicillin		
Strength /formulation		250mg powder for injection
Skin prick test	Concentration	20mg/ml
	Dilution instructions	Reconstitute the 250mg vial with 5mls water for injection to give approx. 50mg/ml solution. 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 injectionto give a 50mg/ml solution. 2. Withdraw 4mls (200mg) and dilute with 6mls sodiumchloride 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	Reconstitute the 600mg vial with 10mls water for injection to give 60mg/ml. 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.

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Appendix 3.2: Dilution instructions

Co-amoxiclav		
Strength /formulation		1.2g, powder for solution for injection /infusion
Skin prick test	Concentration	20mg/ml
	Dilution instructions	Reconstitute with 20mls water for injections to give 50mg /ml 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.

Flucloxacillin		
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.

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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 injectionto give 50mg/ml 2. Withdraw 0.4mls (20mg) and dilute to 1ml with sodiumchloride 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.

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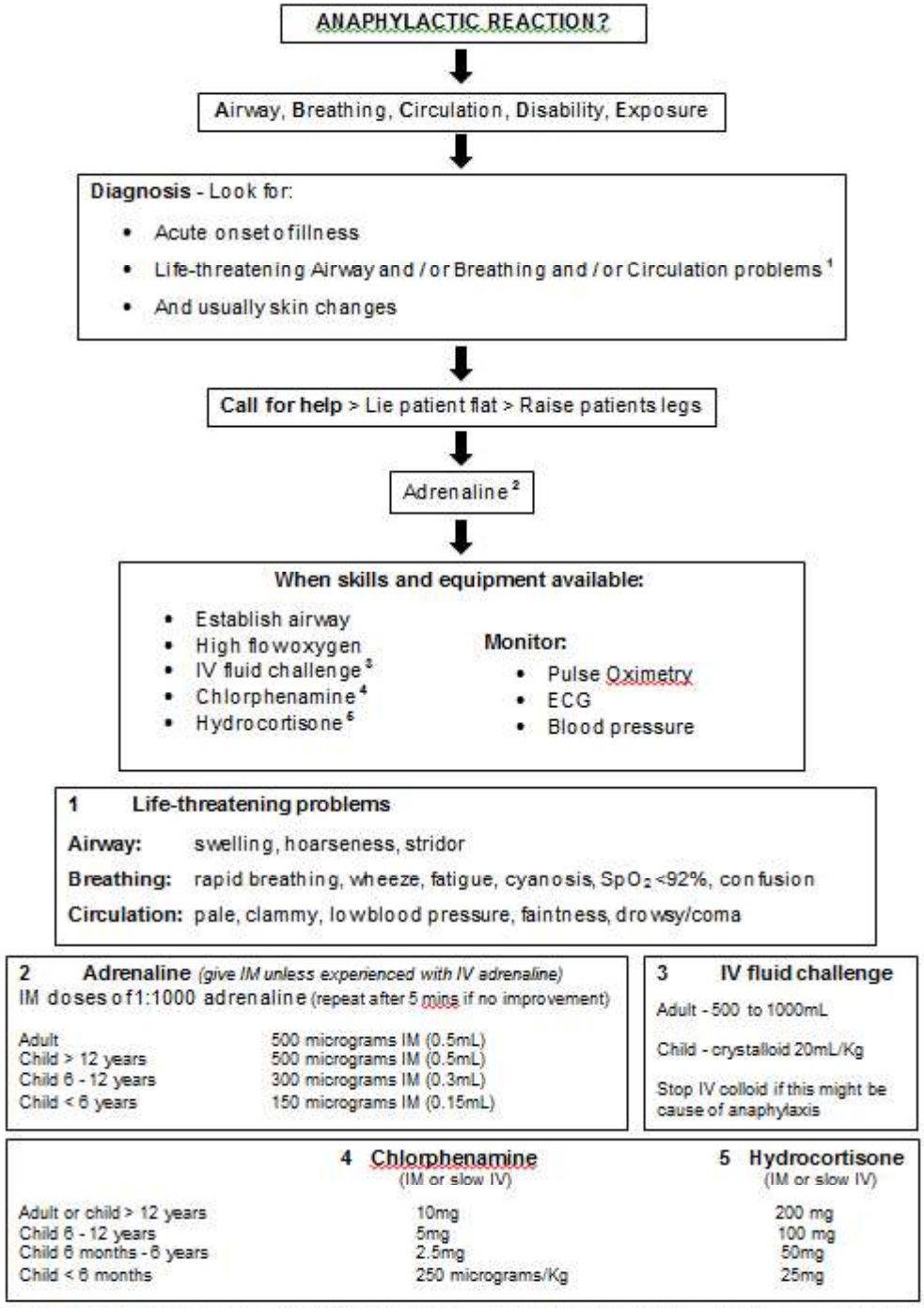
17. Appendix 3.3: Anaphylactic Reaction flowchart



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

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

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18. Appendix 4: ALABAMA SOP, Oral Challenge Test – Penicillin

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

Contributor	**Name**	**Date**	**Signed**
Written by:	Robert White Research Nurse	01.10.20	
Updated by:	Shadia Ahmed Research Fellow	06.05.22	
Approved by:	Dr. Sinisa Savic 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

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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.

19. Appendix 4.1: Signs & Symptoms of allergic reactions in various target organs.

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

20. Appendix 4.2: 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.

21. Appendix 4.3: 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:……..…

22. Appendix 4.4: Oral Challenge Test Prescription Chart (LTHT specific – other sites feel free to use own/localise this version)

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:..... .....Date:...19 Aug 2019.....Approved by:..... Date:.....02 Sep.2019.....

23. Appendix 4.5: **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.

Appendix 4.6 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.

BIBLIOGRAPHY:

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

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

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

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

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

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

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

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,6-9, 12-13

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-3, 4, 7-9, 10, 11, 12-13, 18, 20, 21
Protocol version	#3	Date and version identifier	21
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2, 21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a

Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	11-12
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			

Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	3, 13
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	11-12

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12-13
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7, 16
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	3, 7, 16
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate	10-11

		document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	11, 15, 18

		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 16
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-18
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-18
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	3
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	18

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	3, 7, 12, 18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	3
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix 1 & 2
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A