





# 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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## 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 outcome and antimicrobial resistance. 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 National Health Service 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 1 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

## 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 multicentre design recruiting patients from more than 50 primary care sites from across England will support external validity and National Health Service (NHS) implementation.
- ⇒ Penicillin allergy assessment pathway offers efficient, and economical, one-step testing over current 'gold standard' testing pathways.
- ⇒ ALlergy AntiBiotics And Microbial resistAnce is a complex intervention with an integrated mixed-methods process evaluation to guide future NHS implementation.
- ⇒ By necessity, the trial is open label and delabelling of participants in the intervention arm may influence clinician behaviour across all participants.

will be submitted for publication to an international, peer-reviewed journal.

**Trial registration** ISRCTN20579216.

## 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.<sup>1–5</sup> 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 methicillin-resistant) *Staphylococcus aureus*.<sup>4,5</sup> 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 UK, PEN allergy prevalence is approximately 6%.<sup>5</sup> However, fewer than one in 10 patients with a PEN allergy record are truly allergic after formal assessment.<sup>6-8</sup> 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.<sup>5</sup>

Macrolide, tetracycline, cephalosporin, quinolone and clindamycin prescribing are all more common in primary care patients with a record of PEN allergy compared with those without, and antibiotic prescriptions are almost twice as frequent in patients with a PEN allergy record.<sup>4,5</sup> Evidence from USA and elsewhere suggests that antibiotic allergies affect health outcomes, and increase mortality, length of stay and costs.<sup>5,8</sup> 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 multidrug resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>9-11</sup> 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.<sup>5</sup> 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.<sup>12</sup> 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.<sup>13</sup>

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 have advised that patients should first be skin tested, using prick or intradermal tests, or both.<sup>14,15</sup> The latest US guidelines now recommends for 'low risk' historical penicillin allergic patients, direct oral challenge without preceding skin testing.<sup>16</sup> 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 PEN allergy assessment are not offered the service because of a lack of testing capacity.<sup>17</sup> 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 is consistent with more recent guidelines for non-allergists.<sup>18</sup> 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% to 2%) of immediate or delayed reactions in a pooled analysis of 69 studies.<sup>19</sup> 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 Allergy AntiBiotics And Microbial resistance (ALABAMA) trial (full title: penicillin allergy status and its effect on antibiotic prescribing, patient outcomes and AMR) 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 delabelling of electronic health records. It will evaluate if PAAP is safe and effective in improving patient health outcomes, influencing antibiotic prescribing and supporting health-care implementation. ALABAMA is the first randomised controlled trial to our knowledge that looks at adult PEN allergy testing and delabelling 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 guidelines.<sup>20</sup> 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 Medical Research Council guidelines.<sup>21</sup> The complex intervention is collectively referred to as the '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 delabel, that is, update allergy status in participants' electronic health records appropriately and (3) information for participants to encourage attendance for testing and information pretesting to distinguish side effects (eg, diarrhoea) from true allergic reactions. The development of the physician and participant behavioural intervention component is reported elsewhere.<sup>22</sup>

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 GPs in England. The inclusion

**Table 1** Inclusion and exclusion criteria for the ALABAMA trial

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>▶ Patient is willing and able to give informed consent for participation in the trial</li> <li>▶ Male or female, aged 18 years or above</li> <li>▶ Current penicillin allergy (or sensitivity) record of any kind in their electronic health record</li> <li>▶ Prescribed systemic antibiotics in the previous 24 months</li> </ul>	<ul style="list-style-type: none"> <li>▶ Life expectancy estimated &lt;1 year by GP</li> <li>▶ Unable to attend immunology clinic</li> <li>▶ Unsuitable for entry into testing pathway because:               <ul style="list-style-type: none"> <li>– Allergy history consistent with anaphylaxis to penicillin</li> <li>– 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</li> <li>– Has been formally tested for penicillin allergy in the past and been found to be penicillin allergic</li> <li>– 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</li> <li>– Considered unsuitable for trial participation by the GP for example, because of chaotic lifestyle</li> </ul> </li> <li>▶ Pregnant</li> <li>▶ Breastfeeding mothers</li> <li>▶ Currently taking beta blocker medication, and unable to temporarily withhold these on the day of penicillin allergy testing</li> <li>▶ Currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pretesting</li> <li>▶ Currently taking antihistamines and unable to temporarily withhold these for 72 hours pretesting</li> <li>▶ 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.</li> </ul>

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 have a medical record indicating a penicillin allerg are eligible for the trial.

Note 3, Patients who 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. GP, general practice.

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 GP. 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 SystemOne (an electronic health record system used in primary care that was developed by TPP), thus participating GPs must be using SystemOne. 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 either a face to face or telephone appointment with their GP (or a 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 online supplemental appendices 1 and 2).

Participants must meet the inclusion criteria and have none of the exclusion criteria.

### Patient and public involvement

AMR and antimicrobial allergy lack patient groups/hospital networks/local charities to draw on for patient and public involvement and engagement (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 PEN allergies, including those whose record has been overturned and can now receive penicillins. It also includes those with self-reported (unsubstantiated) PEN allergy.

Our research adopts a codesign 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 (PAT). This is therefore the first trial designed as a 'one stop' efficient allergy assessment for low risk individuals. The guidance to participants about delabelling



also facilitates ease of future NHS implementation and patient uptake of PAT.

PPIE-AF members have been engaged in both the nested pilot and main trial—they reviewed and provided input into the protocol development and the ethics submission. They contributed to the design of the qualitative enquiry and its 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 are broad and include patient groups that are high antimicrobial users. The research team incorporated their views that limiting eligibility to a single group of patients (eg, only those with chronic obstructive pulmonary disease) 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 that 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.

### SystemOne and ALABAMA unit

SystemOne is one of the major electronic health record systems used in primary care in the UK, which was developed by TPP, Leeds, UK, a health technology company. Enrolment of GPs into the ALABAMA trial requires that they use SystemOne as their health record system. Functionality of SystemOne allows the participating GPs to share health records of consented participant and to 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 delabelling 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 GP, 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 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: representation with worsening or non-resolving or new symptoms following treatment with an antibiotic up to 28 days after initial antibiotic prescription (including prescription of antibiotic within 28 days of an index prescription) for predefined infections over at least 1 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 online supplemental 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 and an equivalent analysis by antibiotics class, eg, 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 MRSA infection/colonisation.
6. Effects of PAAP on number of patients with *C. difficile* infection.
7. Cost effectiveness for the PAAP intervention compared with usual care through self-reported health-related quality of life outcomes.

The process evaluation will explore patient and clinician views and experiences of the PAAP, trial procedures and implications on delabelling 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

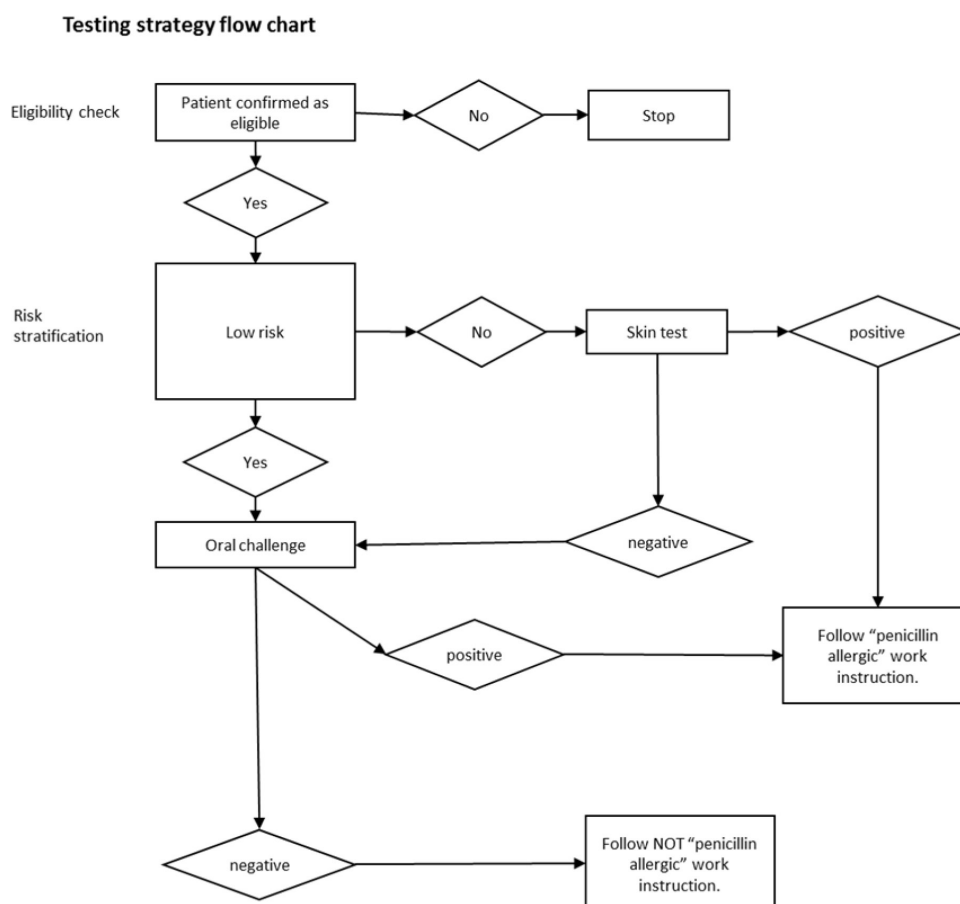
The intervention package includes the PAAP and support materials for clinicians and participants.<sup>22</sup>

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 PAT and motivation to refer participants for a 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 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 online supplemental appendix 3)
- ▶ Stage 3: Oral Challenge Test in hospital clinic/ followed by subsequent doses at home, see online supplemental appendix 4)

Stage 2, if needed, and stage 3 are performed together during half-a-day clinic visit. If there is no initial reaction



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

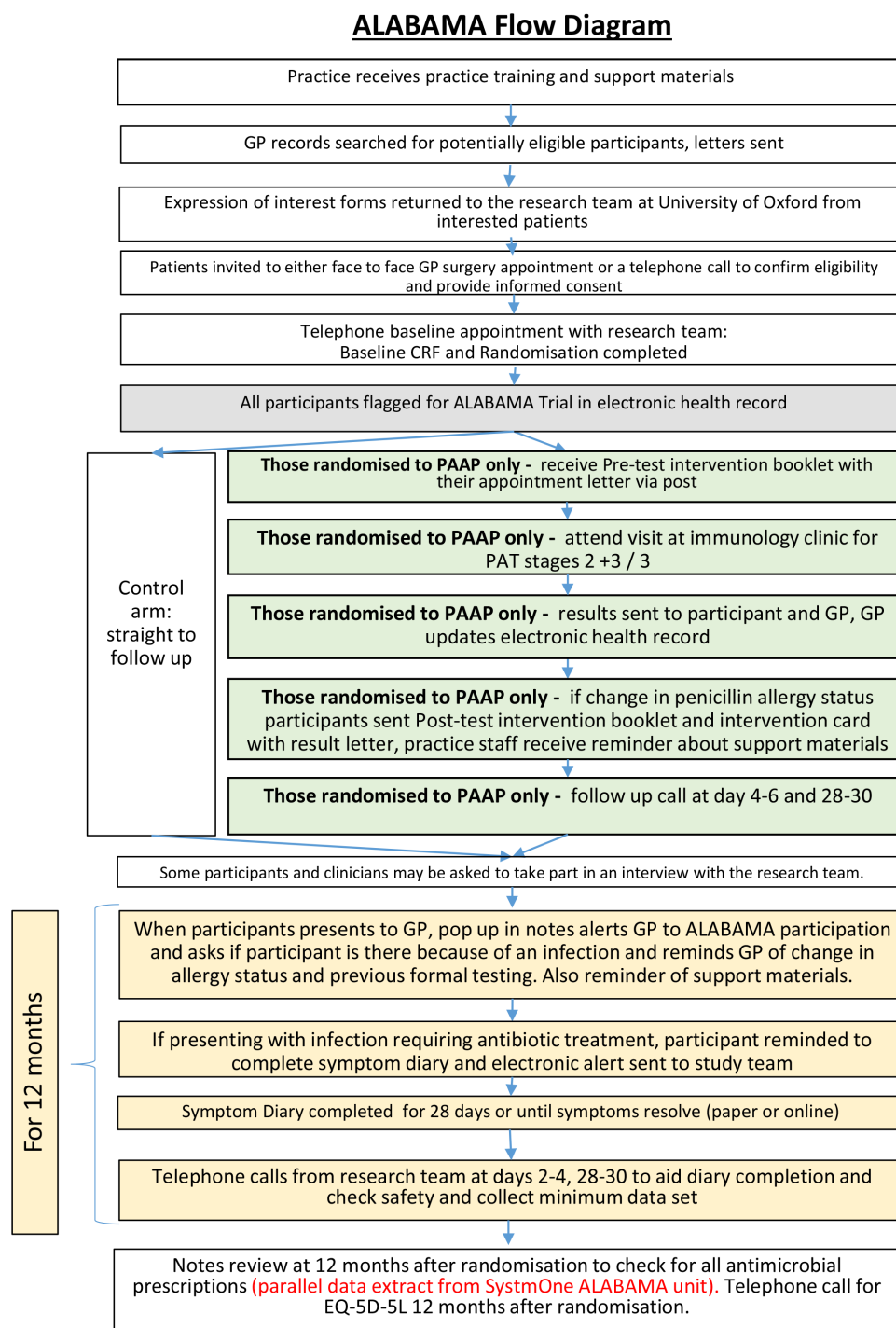
in clinic, the participant will continue the oral challenge test by completing 3 days oral antibiotics at home. [Figure 1](#) shows the PAT flow.

All participants in the intervention arm will be posted a pretest 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



**Figure 2** ALABAMA flow diagram for penicillin allergy assessment pathway (PAAP). ALABAMA, ALlergy AntiBiotics And Microbial resistAnce; GP, general practice; PAT, penicillin allergy test; CRF, case report form.

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 predefined 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 case report forms (CRFs) or directly into the Research Electronic Data Capture (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—<sup>23</sup> 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 predefined infections.

### Linkage with NHS Digital

The SystemOne 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 (Hospital Episode Statistics, HES data), details of antibiotic prescriptions during their admission (GP notes review and secondary care notes review) and mortality data (Office for National Statistics, 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 predefined 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 predefined infections. Anaphylaxis to an antibiotic will be considered an SAE as part of the ALABAMA trial.

Participants in the nested pilot study were also 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 semistructured 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 delabelling; this will include those delabelled but refusing penicillin. Participants and clinicians invited to take part in telephone interviews will be provided with patient information sheets and Informed Consent Forms 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 represcription rate (used as surrogate for treatment response failure) at 1 year between groups at 5% level of significance (two-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 postpandemic climate. The sample size has been adjusted assuming that 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 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, that is, '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.<sup>24 25</sup> 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 healthcare service use will be estimated, respectively, from SystemOne electronic records and the linked individual participant HES 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. Healthcare service costs will be estimated by valuing primary or community care service use using

unit costs from published sources,<sup>26</sup> use of medications with list prices from the British National Formulary 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<sup>27 28</sup> to account for skewness, and adjust for GP, age, number of antibiotic prescriptions in the 12 months prior to randomisation and number of QOF registered diseases, as well as baseline EQ-5D-5L score.<sup>29</sup> 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.<sup>30</sup> 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<sup>31</sup> and joint uncertainty in costs and QALYs will be analysed using cost-effectiveness acceptability curves.<sup>32</sup> Sensitivity analyses will explore variations in key cost and QALY assumptions, including interpolation of utility scores from baseline to 12 month data collection points, disutilities associated with AEs 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 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 on reasonable request.

## DISCUSSION

The importance of AMR and the need to reduce its impact is well recognised.<sup>31</sup> Penicillins are the most commonly prescribed antibiotics<sup>33</sup> 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. Non-penicillin antibiotics 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.<sup>19</sup> 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 on antibiotic prescribing, yield patient benefits, limit AMR/health-care associated infection 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 PAT more efficient. If PAAP is found to be acceptable to patients, this streamlined approach to PAT 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 delabelling, 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 multicentre design which allows recruitment of patients from a number of primary care regions across the UK, 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 an 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 SystemOne 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 AMR 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 delabelling procedures with GPs. As the trial is open label and delabelling 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 SystemOne 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 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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