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

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

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Confidentiality Statement

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

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1. SYNOPSIS

Trial Title	Penicillin allergy status and its effect on antibiotic prescribing, patient outcomes, and antimicrobial resistance. Trial Protocol.	
Internal ref. no. / short title	ALABAMA: **AL**lergy **A**nti**B**iotics **A**nd **M**icrobial resist**A**nce	
Trial Design	Multicentre, two parallel-arm, open label, individually randomised pragmatic trial with a nested-pilot trial	
Trial Participants	Adults (≥18 years of age) with a penicillin allergy record	
Planned Sample Size	Sample size of the trial is between 656 and 848 (including the 96 from the nested pilot)	
Planned Trial Period	5 years	
	Objectives	**Outcome Measures**
Primary Outcome	Effects of PAAP on penicillin prescribing	The proportion of participants who receive prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic (APPENDIX G) up to 12 months post randomisation (SystmOne report/primary care notes review/secondary care notes review/report, patient follow-up calls)
Secondary Outcomes	1. To determine whether the PAAP intervention is clinically effective in improving patient health outcomes.	1. Treatment "response failure" defined as: Re-presentation with worsening or non-resolving or new symptoms following treatment with an antibiotic up to 28 days after initial antibiotic prescription (including re-prescription of antibiotic within 28 days of an index prescription) for predefined infections (SystmOne report, diary), up to 12 months post randomisation.
	2. Effects of PAAP on symptom duration.	2. Duration of symptoms rated 'moderately bad' or worse by patients after antibiotic treatment (diary/research nurse phone calls)
	3. Effects of PAAP on total antibiotic prescribing	3. Total antibiotic use (measured by number of days treatment, number of prescriptions and Defined Daily Dose (DDD).), and analysed by penicillin/non-penicillin and antibiotic class (SystmOne report/primary care notes review/secondary care notes review).

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

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

2. ABBREVIATIONS

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

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

3. BACKGROUND AND RATIONALE

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

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

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

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

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

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

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

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

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

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

4. OBJECTIVES AND OUTCOME MEASURES

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

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

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

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

4.1. Feasibility Outcomes of Nested Pilot Trial

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5. TRIAL DESIGN

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

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

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

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

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

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

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

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

See appendix A for trial flowchart.

6. PARTICIPANT IDENTIFICATION

6.1. Trial Participants

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

6.2. Inclusion Criteria

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

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

6.3. Exclusion Criteria

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

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

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

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

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

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

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

7. TRIAL PROCEDURES

Please see the schedule in Appendix D.

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

7.1. Promotion

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

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

7.2. Site Training

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

7.3. Screening and Eligibility Assessment

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

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

7.4. Informed Consent

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

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

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

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

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

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

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

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

7.5. Baseline Assessments

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

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

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

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

7.6. Randomisation

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

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

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

7.7. Penicillin allergy test Appointment

Please see schedule in Appendix B.

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

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

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

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

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

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

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

7.8. Subsequent Participant Contact

Feasibility outcomes only:

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

Main trial outcomes:

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

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

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

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

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

- Antibiotic consumption and any side effects

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

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

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

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

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

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

7.9. Notes Review

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

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

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

7.10. Interviews

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

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

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

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

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

7.11. Discontinuation/Withdrawal of Participants from Trial

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

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

- Significant protocol deviation
- Withdrawal of Consent

The reason for withdrawal will be recorded in the CRF.

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

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

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

7.12 Implications for Trial Delivery During COVID-19 Pandemic

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

7.13 Definition of End of Trial

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

8. STOP / GO CRITERIA AND PROCESS

8.1. Criteria

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

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

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

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

8.2. Decision Process

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

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

9. BEHAVIOUR CHANGE INTERVENTIONS

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

Patients' intervention materials are likely to include:

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

Clinician intervention materials are likely to include:

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

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

10. SAFETY REPORTING

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

10.1. Adverse Events

10.1.1 Adverse events due to Penicillin Allergy Testing:

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

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

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

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

10.1.2 Post-Antibiotic Prescriptions in primary care:

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

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

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

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

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

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

10.2. Definition of Serious Adverse Events

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

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

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

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

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

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

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

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

10.3. Procedures for Recording Serious Adverse Events

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

10.4. Reporting Procedures for Serious Adverse Events

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

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

11. STATISTICS AND QUALITATIVE ANALYSIS

11.1. Description of Statistical Methods

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

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

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

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

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

11.2. The Number of Participants

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

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

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

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

(1) Adults (over 18 years)

(2) Pen-allergy in electronic health records

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

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

11.3. The Level of Statistical Significance

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

11.4. Criteria for the Termination of the Trial

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

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

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

11.6. Inclusion in Analysis

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

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

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

11.8. Qualitative Analysis

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

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

11.9. Cost-effectiveness Analysis

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

11.9.1 Quality of life and data collection

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

• EQ-5D-5L (EuroQol)[22]

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

• Baseline, pre-randomisation (by telephone)

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

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

11.9.2 Within trial cost-effectiveness analysis

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

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

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

(i) SystmOne (primary/community care)

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

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

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

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

11.9.3 Model based extrapolation beyond the 12 month-trial endpoint

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

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

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

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

11.9.4 Value of Information Analysis

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

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

12. DATA MANAGEMENT

12.1. Source Data

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

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

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

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

12.2. Access to Data

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

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

12.3. Data Recording and Record Keeping

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

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

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

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

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

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

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

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

12.4. SystmOne and ALABAMA Unit

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

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

12.5. Quality Assurance Procedures

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. Guidelines for Good Clinical Practice

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

13.3. Approvals

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

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

13.4. Reporting

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

13.5. Participant Confidentiality

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

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

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

13.6. Expenses and Benefits

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

14. FINANCE AND INSURANCE

14.1. Funding

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

14.2. Insurance

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

15. PUBLICATION POLICY

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

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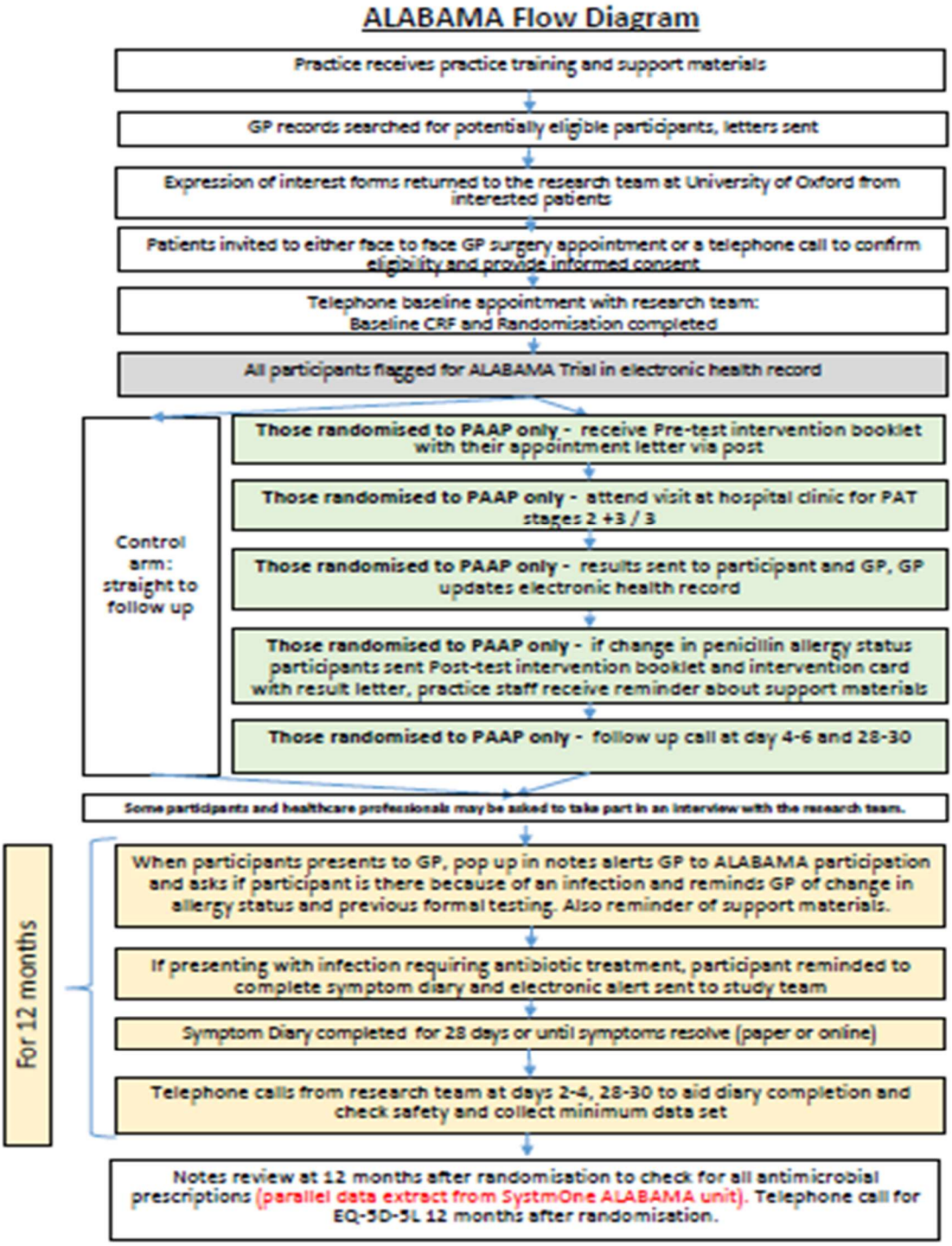
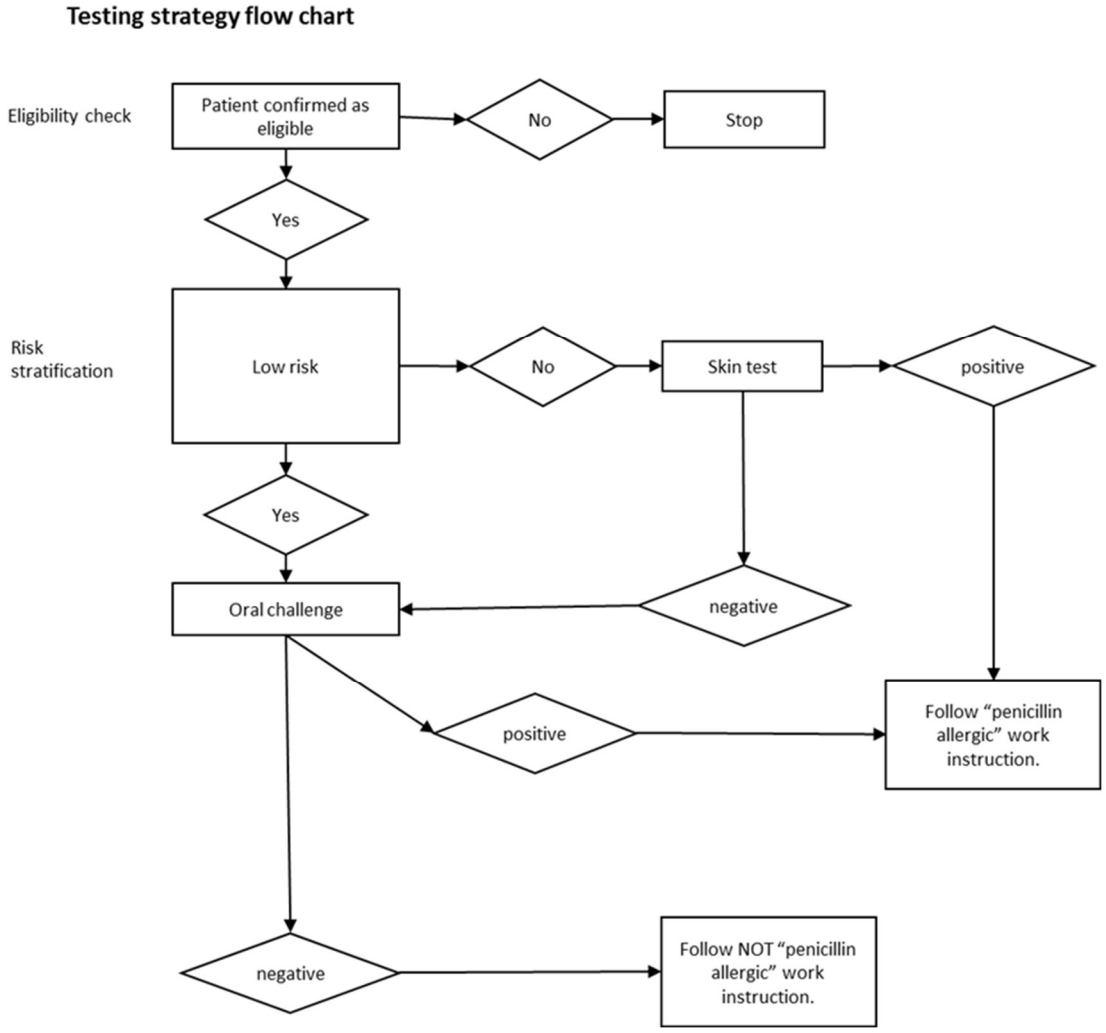
APPENDIX A: TRIAL FLOW CHART



17. APPENDIX B: PAAP FLOW DIAGRAM



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

Summary of operations:

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

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

Stage 3 Oral Challenge Test (OCT) in hospital clinic

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

Background

Assessment of patients with penicillin allergy in specialist clinics is an existing service provided within the NHS. Testing involves:
1) clinical evaluation (allergy and antimicrobial history);
2) skin testing (not needed for all patients);
3) oral challenge test (OCT) (sometimes also called oral provocation tests).

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

Stage 1 PAAP in primary care – Clinical history

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

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

Risks and safety

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

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

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

Risks and safety

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

Stage-3 Oral challenge test in hospital clinic.

Oral challenge tests (OCT, also called drug provocation tests) are needed in patients with a negative skin test because false negative skin tests can occur.[6]
Ideally, we would opt to challenge the patient with the same type of penicillin to which the patient reacted. Unfortunately, this information is frequently lacking, especially in historic cases, where reaction might have occurred many years ago. Since amoxicillin is now the most commonly prescribed antimicrobial of the penicillin class and the most frequent cause of allergic reactions, in cases where the

culprit is unknown we will challenge with amoxicillin. If the patient does not suffer a reaction after this initial challenge they will be given a 3-day course of antimicrobial to take at home and will be followed up by telephone to check for delayed early reactions. If there is no reaction to the oral challenge, patients can then be treated with an oral or parenteral penicillin.

Risks and safety

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

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

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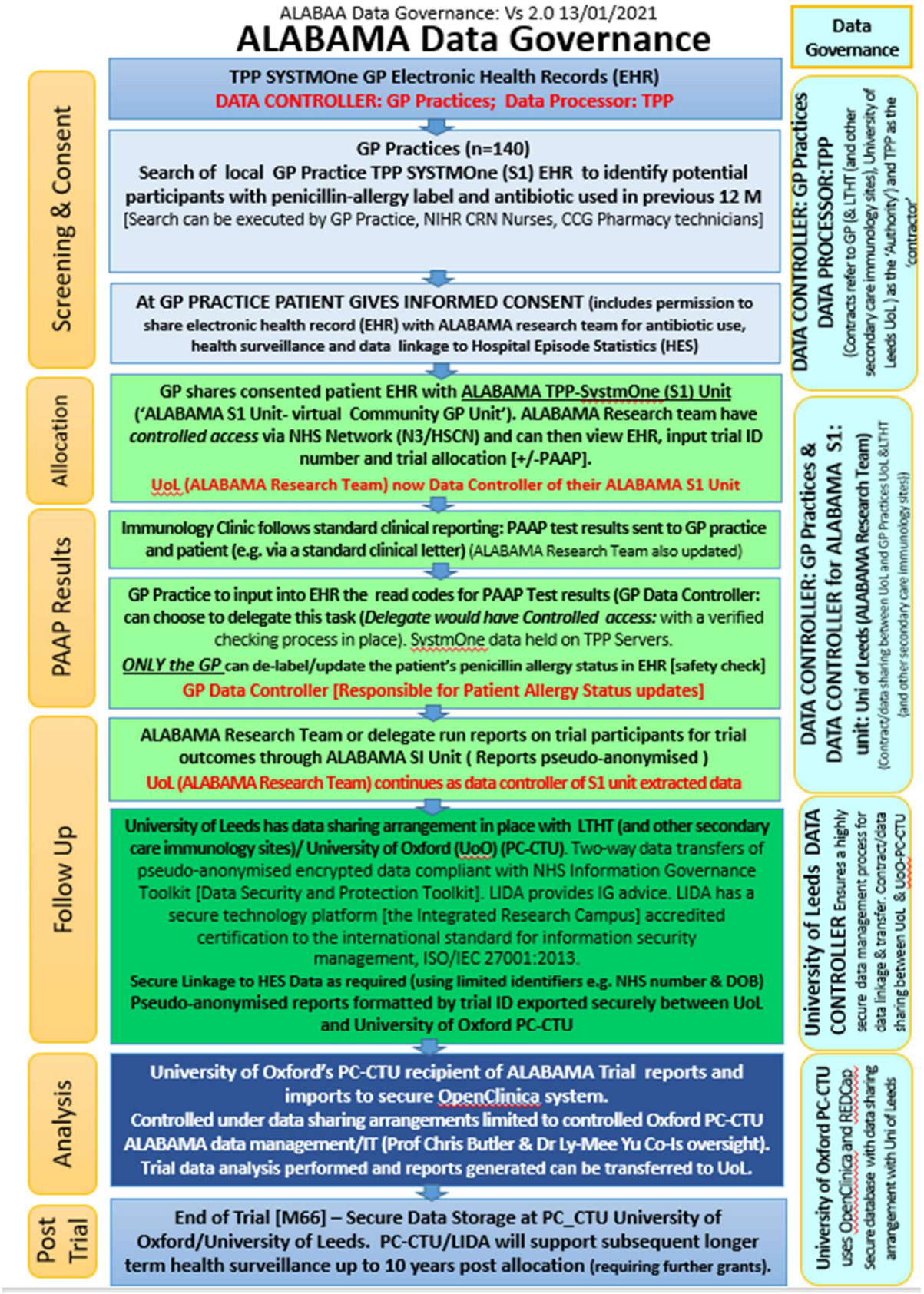
19. APPENDIX D: SCHEDULE OF TRIAL PROCEDURES

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

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



21. APPENDIX F: AMENDMENT HISTORY

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

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

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

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

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

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

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

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

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

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

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