Primary Care Clinical Trials Unit

STATISTICAL ANALYSIS PLAN

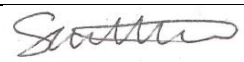
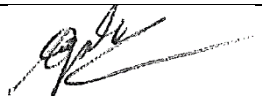
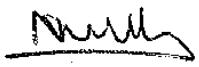
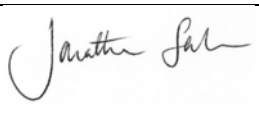
ALABAMA
ALlergy AntiBiotics And Microbial resistAnce

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

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

Version 1.0

9 April 2024

	NAME	TITLE	SIGNATURE	DATE
Written by:	Sam Mort	Trial Statistician		9 April 2024
Reviewed by:	Ushma Galal	Senior Trial Statistician		9 April 2024
Reviewed by:	Nicola Williams	Senior Trial Statistician		15th April 2024
Approved by:	Dr Jonathan Sandoe	Co-Chief Investigator		11th April 2024
Approved by	Prof. Sue Pavitt	Co-Chief Investigator		9th April 2024

VERSION HISTORY

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

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1 INTRODUCTION

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

Short title: ALABAMA: Allergy antibiotics and microbial resistance

Ethics Ref: 19/LO/0176

Sponsor: University of Leeds

Funder: National Institute for Health Research (NIHR)

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

1.1 PREFACE

Chief Investigator: Dr Jonathan Sandoe – j.sandoe@leeds.ac.uk

Co-Chief Investigator: Professor Sue Pavitt – s.pavitt@leeds.ac.uk

Clinical Trial Manager: Kelsey Armitage – kelsey.armitage@phc.ox.ac.uk

Senior Trial Statistician: Ushma Galal – ushma.galal@phc.ox.ac.uk

Lead Statistician: Dr Ly-Mee Yu – ly-mee.yu@phc.ox.ac.uk

Data Manager: Lazarina Engonidou – lazarina.engonidou@phc.ox.ac.uk

1.2 PURPOSE AND SCOPE OF THE PLAN

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

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

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

1.3 TRIAL OVERVIEW

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

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

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

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

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

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

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

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

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

1.4 OBJECTIVES

All the study objectives are described below. A full summary of the study objectives and outcome measures can be found in Appendix I (section 13.1), and the current version of the protocol (version 14.0).

1.4.1 PRIMARY OBJECTIVE

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

1.4.2 SECONDARY OBJECTIVES

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

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

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

2 TRIAL DESIGN

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

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

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

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

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

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

See Appendix III for study flowchart.

2.1 OUTCOME MEASURES

A summary of the study objectives can be found in section 1.4. An outline of the trial procedures and time points can be found in Appendix IV. Only the outcomes which pertain to this statistical analysis plan will be listed here.

2.1.1 PRIMARY OUTCOME – EFFECTS OF PAAP ON PENICILLIN PRESCRIBING

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

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

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

2.1.2 SECONDARY OUTCOMES

2.1.2.1 TREATMENT "RESPONSE FAILURE"

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

2.1.2.2 DURATION OF SYMPTOMS RATED 'MODERATELY BAD' OR WORSE

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

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

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

2.1.2.3 ANTIBIOTIC PRESCRIPTIONS

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

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

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

2.1.2.3.1 NUMBER OF ANTIBIOTIC PRESCRIPTIONS

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

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

2.1.2.3.2 NUMBER OF DAYS OF TREATMENT

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

2.1.2.3.3 DEFINED DAILY DOSE (DDD)

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

2.1.2.4 HOSPITAL ADMISSIONS

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

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

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

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

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

2.1.2.5 MORTALITY RATES

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

2.1.2.6 MRSA INFECTION/COLONISATION

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

2.1.2.7 *CLOSTRIDIOIDES DIFFICILE* INFECTION

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

2.1.2.8 DE-LABELLING AT 3 MONTHS POST RANDOMISATION

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

2.1.2.9 DE-LABELLING AT 12 MONTHS POST RANDOMISATION

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

2.2 TARGET POPULATION

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

2.2.1 INCLUSION CRITERIA

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

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

2.2.2 EXCLUSION CRITERIA

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

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

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

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

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

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

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

2.3 SAMPLE SIZE

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

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

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

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

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

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

2.4 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

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

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

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

3 ANALYSIS – GENERAL CONSIDERATIONS

3.1 DESCRIPTIVE STATISTICS

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

3.2 CHARACTERISTICS OF PARTICIPANTS

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

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

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

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

3.3 DEFINITION OF POPULATION FOR ANALYSIS

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

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

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

3.4 POOLING OF INVESTIGATIONAL SITES

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

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

3.5 DATA MONITORING COMMITTEE AND INTERIM ANALYSES

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

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

No interim analysis for efficacy was planned for this study.

4 PRIMARY ANALYSIS

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

4.1 PRIMARY OUTCOME

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

4.2 HANDLING MISSING DATA

Missing data will be reported, with reasons where available. The mixed effects regression model assumes data is missing at random (MAR), however the mechanism of missing data will be explored. The baseline characteristics listed in section 3.2 (except those that were patient reported, and the ones from Sortition used in the randomisation) will be summarised for both randomised groups, split depending on if the primary outcome is available or missing. A logistic regression model will explore any association between each baseline characteristic and the availability of the primary outcome. Covariates found to be predictive of missingness ($P<0.05$) will be included in the analysis model in a sensitivity analysis of the primary outcome (see section 6). If the primary outcome is available for all participants this will not be conducted.

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

4.3 HANDLING OUTLIERS

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

4.4 MULTIPLE COMPARISONS AND MULTIPLICITY

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

5 SECONDARY ANALYSIS

5.1 BINARY OUTCOMES

The binary secondary outcomes:

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

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

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

5.2 CONTINUOUS OUTCOMES

The continuous secondary outcomes:

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

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

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

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

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

5.3 COUNT OUTCOMES

The count secondary outcomes:

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

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

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

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

6 SENSITIVITY ANALYSIS

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

6.1 AS TREATED (AT)

Participants were analysed in their randomly assigned intervention arm for the primary analysis regardless of whether they received the intervention or not. A sensitivity analysis will be conducted analysing participants depending on whether they received the allocated intervention or not. The definition of the “as treated” (AT) analysis population is described in section 3.3.

The model used in the primary analysis (section 4.1) will be re-run on the AT group, with age, number of antibiotic prescriptions in the 24 months (12 months for those recruited to the nested pilot study) prior to randomisation, and the number of QOF registered diseases as fixed effects. GP practice will be included as a random effect. The adjusted relative risk between the AT groups and the corresponding 95% confidence intervals will be obtained from the model and reported alongside the associated P-value.

6.2 FACTORS THAT PREDICT MISSINGNESS

A logistic regression analysis, described in section 4.2 will be conducted to investigate factors (if any) that are predictive of non-response of the primary outcome. If any factors are associated with non-response, the model used in the primary analysis (section 4.1) will be re-run with these factors included in the model as fixed effects, alongside randomised group, age, number of antibiotic prescriptions in the 24 months prior to randomisation (12 months for those recruited to the nested pilot study), and the number of QOF registered diseases as fixed effects, and GP practice as a random effect. The adjusted relative risk between the randomised groups and the corresponding 95% confidence intervals will be obtained from the model and reported alongside the associated P-value.

6.3 EXCLUDED PARTICIPANTS WHO DID NOT HAVE COMPLETE FOLLOW-UP

Participants recruited towards the end of the recruitment period may not have been followed-up for the full 12 months of the planned follow-up period. If there are any participants who were not followed-up for 12 months, the primary analysis (section 4.1) will be re-run with these participants excluded from the analysis.

6.4 EXCLUDING PARTICIPANTS WHO HAD DELAYED PAAP

There may be cases were a participant who was randomised to PAAP did not receive PAAP for quite some time. The primary analysis (section 4.1) will be re-run with the participants who were delayed in receiving the PAAP by more than 3 months (90 days) excluded from the analysis population.

7 SUBGROUP ANALYSES

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

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

The primary analysis (see section 4.1) will be rerun with an additional two-way interaction between randomised group and subgroup as a fixed effect. The adjusted relative risk between the randomised groups in each level of the subgroup and the corresponding 95% confidence intervals will be obtained from the model which will be reported alongside the associated P-value for the interaction. The results of the subgroup analyses will be presented in a forest plot.

8 EXPLORATORY ANALYSIS

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

9 SAFETY ANALYSIS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1. Penicillin Allergy Assessment (PAA)

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

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

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

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

10 DESCRIPTIVE ANALYSIS

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

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

11 VALIDATION

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

12 CHANGES TO THE PROTOCOL OR PREVIOUS VERSIONS OF SAP

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

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14 APPENDICES

14.1 APPENDIX I. OBJECTIVES AND OUTCOME MEASURES

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

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

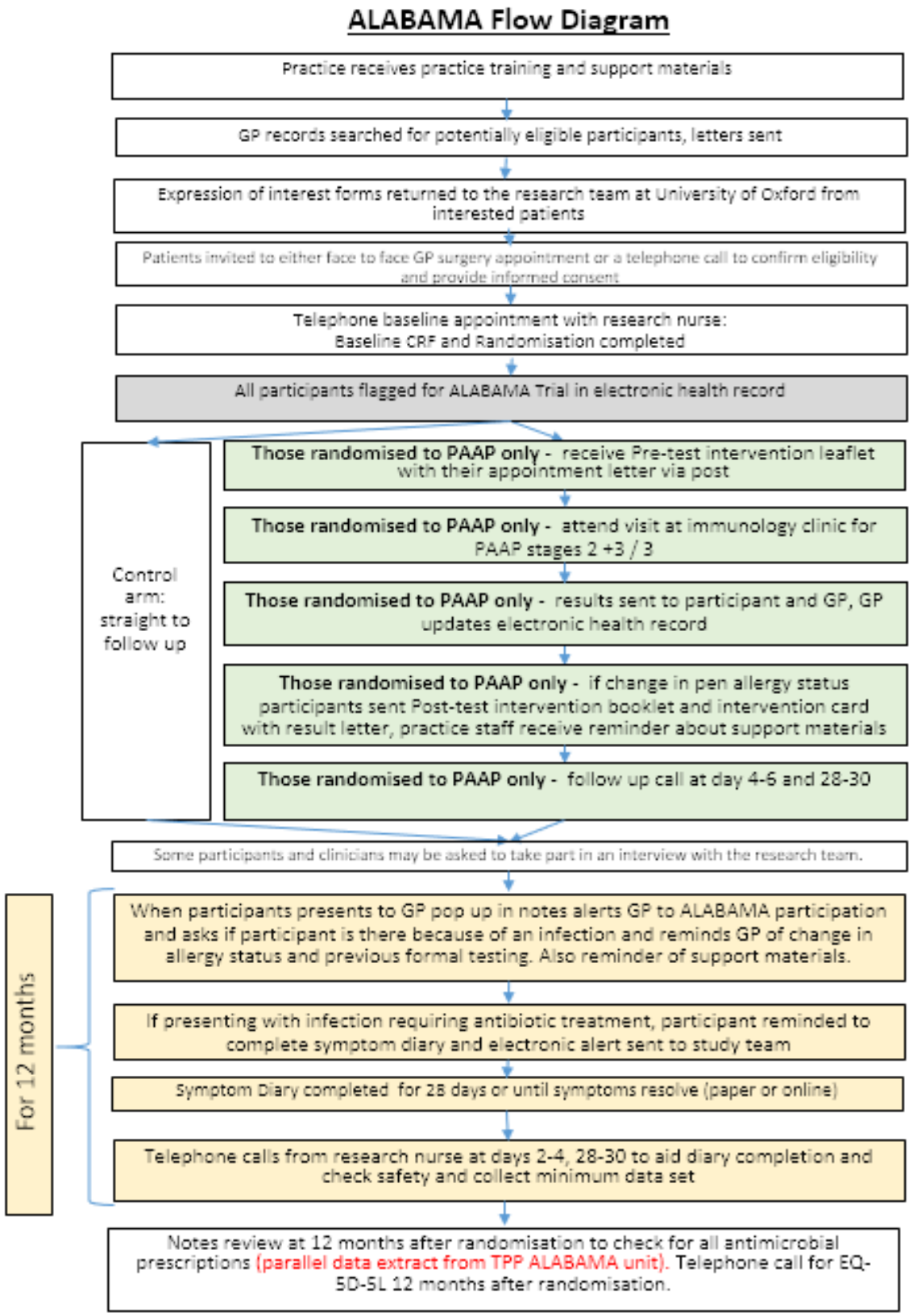
Objectives	Outcome Measures	Timepoint(s) (if applicable)
10. To measure the influences on patient behaviour change regarding consuming penicillin following a negative test result	10. Change in self-reported behaviour and influences on behaviour by patients	10. Participant allergy belief questionnaire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

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

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

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

14.3 APPENDIX III. TRIAL FLOW DIAGRAM



14.4 APPENDIX IV. SCHEDULE OF TRIAL PROCEDURES

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

14.5 APPENDIX V. DUMMY BASELINE TABLE

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

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

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

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

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

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

14.6 APPENDIX VI. FLOW DIAGRAM OF TRIAL PARTICIPANTS