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Extended Research Article

Penicillin allergy assessment pathway to improve antibiotic use: the ALABAMA intervention development, RCT, process and cost-effectiveness evaluation

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Abstract

Background: People with penicillin allergy labels receive more antibiotics, different antibiotics and have worse health outcomes when compared to people without a penicillin allergy label.

Objective: To determine if a pre-emptive penicillin allergy assessment pathway can remove incorrect penicillin allergy labels, improve antibiotic prescribing and health outcomes, and is cost-effective.

Design: A multi-work package programme to develop and evaluate a complex intervention (penicillin allergy assessment pathway), including rapid literature review (work package 1.1), behaviour change material development (work packages 1.2 and 1.3), medical record updating processes (work package 1.4), a pragmatic randomised controlled trial (work package 2.1) with nested pilot (work package 1.5), health economic evaluation (work package 2.2) and process evaluation (work package 2.3).

Setting: English general practices and hospital sites in West Yorkshire, South Yorkshire and Cornwall.

Participants: Trial participants were adult general practice patients with a record of penicillin allergy. Interview subjects were general practitioners and healthcare workers involved in penicillin allergy assessment, trial and non-trial participants with a penicillin allergy.

Interventions: Complex intervention involving: identification of appropriate participants, risk stratifying and testing for penicillin allergy, promoting behaviour change and updating medical records.

Main outcome measures: Penicillin prescribing, total antibiotic prescribing, treatment response failure, duration of symptoms, hospital admission/length of stay, mortality, meticillin-resistant *Staphylococcus aureus* status and *Clostridioides difficile* infection, penicillin allergy de-labelling' rates. People's views about penicillin allergy and testing.

Results:

Work package 1.1: Our review showed that patients had some worries about penicillin allergy testing but could see advantages. Clinicians were uncertain about referral criteria. Clinicians were wary about prescribing and patients were wary about consuming penicillins after a negative test. Fear of subsequent reactions were drivers. This informed WP1.3 development of resources to aid penicillin allergy assessment.

Work package 1.2: Our qualitative research showed that patients were unaware of the benefits of penicillin allergy testing. Experience of negative effects of penicillin allergy labels motivated patients to be tested. Clinicians were reluctant to de-label patients using clinical judgement alone. Clinicians and patients were generally supportive of penicillin allergy testing. This informed work package 1.3.

Work package 1.3: Materials were developed to increase knowledge of penicillin allergy testing, support beliefs about the importance of testing, and to increase confidence in performing the behaviours safely by providing a supportive environment. Materials comprised information booklets for general practitioners and participants, electronic health record (SystmOne) pop-ups, post testing result cards, trial work instructions/training material, participant and clinician letters.

Work package 1.4: General practitioners were happy to update medical records after a negative test result. 'Marking in error' was used to update SystmOne if a participant had a negative penicillin allergy test, which removed allergy alerts but maintained an audit trail. General practitioner trial training/procedures informed general practitioners how to update records. SystmOne functions developed to facilitate de-labelling.

Work package 1.5: Target recruitment for the pilot target was achieved. Identification of suitable patients from SystmOne was successful. Willingness of general practitioners to refer patients and participants to undergo testing was demonstrated. A data-secure 'ALABAMA unit' was set up within SystmOne. Processes for referring and following-up participants via the ALABAMA unit were established. Low symptom diary completion rate indicated case note data would also be needed.

Work package 1.6: During the nested pilot trial, multiple measures were developed, approved and implemented to maximise recruitment for the main trial; including additional testing sites were recruited in South Yorkshire and Cornwall.

Work package 2.1: The randomised controlled trial found there was a statistically significant increase in the number of patients de-labelled and penicillin prescribing was statistically significantly increased (adjusted relative risk 5.26) and median total defined daily dose of antibiotics was reduced by 25% in the intervention group. There were no significant differences in other secondary outcomes.

Work package 2.2: Within-trial assessment indicated the assessment pathway was likely to be cost-effective. The cost-effectiveness modelling suggested the net benefit of testing was high but uncertainties were high. The value of information studies indicated another trial including health outcomes was worthwhile.

Work package 2.3: General practitioners were motivated to join the trial because of perceived benefit to patients. General practitioners were positive about the trial design/delivery and support from the trial team. Many participants sought clarity about penicillin allergy status. Participants reported feeling safe and well looked after during testing. Most participants accepted test results and were relieved to receive a negative test that enabled them to take penicillin. The process evaluation provided important information on how to improve future National Health Service implementation. Specifically, the need for a safe, accessible and reliable service where general practitioners need to be provided with step-by-step guidance how to identify patients with different risk of true penicillin allergy to facilitate onward referral/assessment. The resources developed within the programme could be used as part of wider implementation to encourage and support patients and healthcare workers to engage with and deliver penicillin allergy assessment.

Limitations: The coronavirus disease discovered in 2019 pandemic affected recruitment and reduced the sample size meaning the primary outcome had to be agreed and changed to an antibiotic prescribing outcome. The research was conducted using functionality developed in SystmOne; there needs to be consideration of how to maximise knowledge transfer this functionality to other electronic health record systems.

Conclusion: The pre-emptive penicillin allergy assessment pathway was safe, increased penicillin prescribing reduced overall antibiotic prescribing, produced sustained de-labelling and was cost-effective. The assessment pathway was well received by participants and general practitioners. We conclude that patients who are recent users of antibiotics and are lower risk for true penicillin allergy would likely benefit from penicillin allergy assessment.

Future work: A larger trial is needed to determine if penicillin allergy assessment can improve patient health outcomes. Implementation studies are needed to determine how best to safely embed penicillin allergy assessment into clinical practice and to widen access beyond the current referral guidelines.

Trial registration: This clinical trial is registered as Current Controlled Trials ISRCTN20579216 and ClinicalTrials.gov NCT04108637.

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List of abbreviations

AMR	antimicrobial resistance
CDI	*Clostridioides difficile* infection
CRN	Clinical Research Network
DMEC	Data Management and Ethics Committee
EHR	electronic health record
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
ETC	excess treatment cost
GDPR	General Data Protection Regulation
GP	general practitioner
HCAI	healthcare associated infection
MRSA	meticillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Care Excellence
NP	nested pilot
PAAP	penicillin allergy assessment pathway
PAL	penicillin allergy label
PAT	penicillin allergy testing
PE	process evaluation
PPIE	patient and public involvement and engagement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
SoECAT	Schedule of Events Cost Attribution Template
TPP	The Phoenix Partnership
TSC	Trial Steering Committee
UCC	usual clinical care
WP	work package

Plain language summary

Background

Antibiotic overuse has resulted in more infections caused by antibiotic-resistant bacteria which make people ill for longer and increases their risk of death. New ways to reduce antibiotic prescribing are needed. Many people have a penicillin allergy label which means doctors avoid first-line penicillin antibiotics and prescribe alternatives, which may not work as well, may cause more side-effects, can be expensive, and can lead to more antibiotic resistance in bacteria. Most people with a penicillin allergy label are not actually allergic when tested and can safely take penicillins.

Aim

To find out if a pathway for assessing people with a penicillin allergy label allows better use of penicillin and other antibiotics, improves health outcomes, and is good value for money.

Methods

We used a mixture of research methods including interviews with patients and doctors and focus groups with experts to come up with a trial design that would work and be acceptable to patients and doctors. We developed ways to help patients get tested and for them to receive penicillins if they were not allergic. We carried out a clinical trial of an allergy testing pathway in comparison to usual clinical care to really find out if it was beneficial. The trial had to be reduced in size because of coronavirus disease discovered in 2019.

Results

Many people were not aware of the harms linked to penicillin allergy labels. Patients and doctors generally thought penicillin allergy assessment was a good idea but they did not know much about it. Trial materials helped patients and doctors understand the processes. The trial found the penicillin allergy assessment pathway was safe, increased penicillin prescribing fivefold, reduced all antibiotic prescribing, and was probably cost-effective. The pathway was well received by patients and general practitioners.

Conclusions

Penicillin allergy assessment benefits patients by safely and efficiently allowing them to receive first-line penicillin treatment and by reducing the amount of antibiotics they need.

Scientific summary

Background

The importance of antimicrobial resistance (AMR) and the need to reduce its impact is well recognised. One way to reduce AMR is to improve the quality of antibiotic use as well as reduce the quantity of antibiotics used. Penicillins are first-line therapy for many common infections, but patients with a penicillin allergy label (PAL) are much less likely to be prescribed penicillins (West RM, Smith CJ, Pavitt SH, Butler CC, Howard P, Bates C, *et al*. 'Warning: allergic to penicillin': association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing and health outcomes. *J Antimicrob Chemother* 2019;**74**:2075–82. https://doi.org/10.1093/jac/dkz127, Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. *BMJ* 2018;**361**:k2400. https://doi.org/10.1136/bmj.k2400) and may therefore be disadvantaged.

Penicillin allergy labels are common, affecting about 6% of the English population. (West *et al*. 2019) Importantly, fewer than 10% of these patients are truly allergic (Powell N, Stephens J, Kohl D, Owens R, Ahmed S, Musicha C, *et al*. The effectiveness of interventions that support penicillin allergy assessment and delabeling of adult and pediatric patients by nonallergy specialists: a systematic review and meta-analysis. *Int J Infect Dis* 2023;**129**:152–61. https://doi.org/10.1016/j.ijid.2022.11.026). Spurious PALs arise for many reasons including side effects and symptoms related to the infection requiring antibiotic treatment being mislabelled as allergies; health record systems not easily allowing distinction of allergic symptoms and side effects and allergy waning over time. Consequently, a significant proportion of the population are restricted access to highly effective penicillins.

Several negative health outcomes have been associated with PALs. Penicillin allergy records are associated with AMR; for example, 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) (West *et al*. 2019, Blumenthal *et al*. 2018, Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin 'allergy' in hospitalized patients: a cohort study. *J Allergy Clin Immunol* 2014;**133**:790–6. https://doi.org/10.1016/j.jaci.2013.09.021). This appears to be because patients with a penicillin allergy are usually prescribed alternative antibiotics like fluoroquinolones, macrolides and clindamycin (Blumenthal *et al*. 2018). 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). Systematic review evidence indicates that antibiotic allergies affect health outcomes, increasing mortality, length of hospital stay, and costs (Krah NM, Jones TW, Lake J, Hersh AL. The impact of antibiotic allergy labels on antibiotic exposure, clinical outcomes, and healthcare costs: a systematic review. *Infect Control Hosp Epidemiol* 2021;**42**:530–48. https://doi.org/10.1017/ice.2020.1229). 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, and deliver NHS cost savings. The focus of ALABAMA was spurious or 'false-positive' penicillin allergy records, and whether a trial of a complex intervention aimed at correcting such records is safe, clinically effective and cost-effective.

Objectives

Workstream 1: Intervention development and feasibility

Objective 1a: Development of the complex intervention (work packages 1.1, 1.2, 1.3, 1.4)

To design a complex intervention to support and provide a PAAP for primary care patients with a record of a penicillin allergy, following Medical Research Council guidelines.

Objective 1b: Feasibility (work packages 1.5 and 1.6)
To undertake a nested pilot (NP) trial to assess safety, acceptability and practicality of delivering a trial of the PAAP intervention.

Workstream 2: Evaluation and implementation of the penicillin allergy assessment pathway intervention

Objective 2a: Full trial (work package 2.1)
To conduct a randomised clinical trial of the PAAP intervention versus usual clinical care to assess impact on antimicrobial prescribing and health outcomes.

Objective 2b: Cost-effectiveness: to determine whether the penicillin allergy assessment pathway intervention is cost-effective (work package 2.2)

Objective 2c: Process evaluation: to conduct a process evaluation of the main trial to assess implementation of the penicillin allergy assessment pathway intervention and to produce recommendations for wider National Health Service uptake (work package 2.3)

Work packages, methods and results

Workstream 1: Complex intervention development and feasibility evaluation

Work package 1.1: Rapid review of evidence regarding patient/prescriber views of penicillin allergy and behaviour change in relation to allergy testing and antibiotic prescribing

Aim
To synthesise published evidence of patients' and/or clinicians' views and experiences of penicillin allergy testing (PAT) services and influences on antibiotic prescribing behaviour in the context of penicillin allergy.

Findings
Patients had some worries about PAT but could see advantages. Clinicians were uncertain about referral criteria. Clinicians were wary about prescribing and patients were wary about consuming penicillins after a negative test. Fear of subsequent reactions were drivers.

Limitations
Limited numbers of cross-sectional survey studies were identified, assessing clinical aspects of penicillin allergy tests and accuracy. A full systematic review might have found more studies. Lack of quality assessment and double-checking could have introduced a bias.

What this meant
For key behaviours to change regarding engagement with penicillin allergy assessment, a behavioural intervention would need to address these issues and target both patients and general practitioners (GPs).

Work package 1.2: Qualitative study of patient/prescriber attitudes to penicillin allergy and penicillin allergy testing

Aims
To identify primary care clinician and patient views on barriers and enablers to PAT and subsequent antibiotic use.

Findings
Patients were generally unaware of the benefits of PAT. Experience of the negative effects of PALs motivated patients to be tested. Clinicians were reluctant to de-label patients using clinical judgement alone. Clinicians had limited

experience of referring patients with PALs for assessment and testing processes. Clinicians described numerous potential benefits of testing. Patients who had been tested reported benefits of the process. There was uncertainty about who should ensure the patient understood allergy test results among GPs.

Limitations

This was a qualitative study with a purposeful sample that recruited from one region in England; the results should be interpreted cautiously in terms of their transferability to other settings.

What this meant

The behaviour change component of the intervention would need to provide information for both patients and GPs about PAT and the benefits of penicillin allergy assessment. The GP facing component would need to cover referral processes and interpretation of test results.

Work package 1.3: Development of intervention materials to support patient and clinician engagement with penicillin allergy assessment pathway

Aim

To develop intervention materials to support the implementation and uptake of PAAP by clinicians and patients.

Results

To support clinicians and patients in undertaking the desired behaviours involved in the PAAP, materials were developed that were intended to increase knowledge of PAT, support beliefs about the importance of testing and the importance of tackling AMR and to increase confidence in performing the behaviours safely by providing a supportive environment. Materials comprised separate information booklets for GPs and patients, electronic health record pop-ups, post testing result cards for patients, trial work instructions and training material, patient and clinician letters. Feedback from think-aloud interviews identified changes required to draft intervention materials in order to increase acceptability and feasibility of the PAAP with patients and clinicians.

Limitations

A limitation of the ALABAMA intervention package is uncertainty about its wider application outside the trial. The intervention was centred around functionality within SystmOne (an electronic medical record system widely used in general practice). The intervention package developed within ALABAMA will need to be modified to allow full functionality in other GP electronic health records systems.

What this meant

Behaviour change materials were prepared and ready for embedding into the trial intervention and testing in the pilot trial.

Work package 1.4: Design of systems and processes for recording/updating penicillin allergy records

Aim

To determine how best to update penicillin allergy records to maximise the impact of PAT while maintaining patient safety.

Results

Qualitative interview research found GPs were happy to update medical records after a negative test result provided there were clear directions. GPs also expressed concerns about patients becoming relabelled as penicillin allergic. GP trial training and standard operating procedures were developed to inform GPs how to update records. To improve de-labelling, a new function in SystmOne was utilised to send a 'task' to the GP. Processes were developed to update secondary care records in line with primary care.

Limitations
The processes that were developed were specific to the SystmOne electronic health record system and equivalent functionality would need to be established for other electronic health record systems.

What this meant
Processes for updating primary and secondary health records were ready for testing in the pilot trial.

Work package 1.5: Assessment of the feasibility of delivering a randomised controlled trial of the penicillin allergy assessment pathway intervention versus usual clinical care

Aim
To undertake a NP randomised controlled trial (RCT) with feasibility outcomes to assess safety, acceptability and practicality of delivering a trial of the PAAP intervention.

Results
Before having to pause trial activities in April 2020, due to coronavirus disease discovered in 2019 (COVID-19), 81 participants were consented satisfying stop/go criteria. The Data Management and Ethics Committee (DMEC) reviewed safety data on completion of the NP trial and concluded it was safe to continue to main trial.

Feasibility outcomes: Identification of suitable patients from GP electronic health records was successful. Willingness of GPs to refer patients to PAAP and participants to undergo testing was demonstrated. The processes of setting up a data-secure 'ALABAMA unit' within the SystmOne electronic health record system, referring participants into the unit, allocating to treatment group, and follow-up via the ALABAMA unit were built, tested and piloted. Research nurse follow-up of primary events and post testing safety checks were demonstrated to be feasible. Symptom diary completion rate was low.

Limitations
Onset of the COVID-19 pandemic delayed randomisation and testing for some consented participants. COVID-19 interrupted follow-up for only a minority, meaning the planned monthly telephone calls did not occur for one participant. Many patients actively avoided contacting GPs during the pandemic, alongside socialisation restrictions, and use of face mask that collectively resulted in antibiotic prescribing falling during this period, potentially reducing the number of primary events. (Primary events were antibiotic prescriptions for a pre-defined list of infections which prompted the participant to complete a symptom diary for trial outcome data analysis.)

What this meant
As the pilot recruitment target was achieved, the independent DMEC and Trial Steering Committee (TSC) recommended automatic progression to main trial. The ALABAMA trial restarted 1 November 2020. Given low diary completion rates, it was clear that the 28–30 follow-up call would be needed to ensure 'treatment response failure' data could be captured. This confirmed SystmOne could be used to deliver key elements of the ALABAMA trial.

Work package 1.6: Understanding recruitment to ALABAMA penicillin allergy assessment pathway trial

Aims
To optimise recruitment to the trial and understand why patients wanted to participate in the trial.

Results
Initially there were low rates of conversion from expression of interest to consent. During the NP trial, the following measures were approved and implemented to maximise recruitment:

- NHS research staff were seconded to the local GP confederation enabling them to work as part of the GP practice team and follow up non-responders/pre-consented participants.
- Verbal telephone consent, which saved GP/participants' time.

- Non-responder letters were sent to patients who did not respond to the first mail-out.
- Up to two follow-up calls could be made to non-responders by research nurses.
- Posters for display in GP practices and local pharmacies, to improve awareness.
- Non-responder follow-up (via mail or telephone) had a noticeable positive impact on response rates.
- As part of our recruitment strategy for the main trial we recruited additional sites: South Yorkshire and Cornwall.

Limitations

Formal analysis of the different approaches used to improve recruitment was not undertaken, rather an iterative consensus process was used.

What this meant

We moved to recruit to the main trial with an improved recruitment strategy and trial processes that had been refined and tested. Measures were put in place to allow recruitment to continue in spite of COVID-19.

Workstream 2: Evaluation and implementation of the penicillin allergy assessment pathway intervention

Work package 2.1: Randomised controlled trial of the safety, clinical and cost-effectiveness of the penicillin allergy assessment pathway intervention versus usual clinical care, on health outcomes, antimicrobial prescribing and antimicrobial resistance

Aim

To determine whether a pre-emptive (carried out in advance of need) PAAP intervention is safe and clinically effective in improving antibiotic prescribing and patient health outcomes in patients with a record of penicillin allergy in their primary care electronic health records.

Results

Penicillin allergy assessment pathway resulted in a statistically significant increase in penicillin allergy de-labelling [risk difference 87.4% (84.1 to 90.9), *p*-value < 0.0001] and also in penicillin prescribing [adjusted relative risk 5.26, 95% confidence interval (CI) 3.03 to 9.18]. Total prescriptions and total defined daily doses were reduced (adjusted median difference −3.17, 95% CI −6.11 to −0.23). Prescriptions of non-penicillin antibiotics reduced in the PAAP group compared to the usual care group. There were no important differences in safety outcomes. The PAAP intervention did not significantly affect mortality, hospital admissions or hospital length of stay, duration of symptoms, MRSA or *Clostridioides difficile* infection (CDI) rates or treatment response failure rates. The PAAP intervention significantly increased de-labelling at 3 and 12 months.

Limitations

The trial took place during the COVID-19 pandemic which impacted on recruitment. The primary outcome was changed, with full consideration and agreement of the DMEC and funder, from 'treatment response failure' to one measuring penicillin prescribing. In addition, the trial may underestimate the effect of the intervention as visits to GPs and antibiotic prescribing were both reduced during the COVID-19 pandemic. The trial was open label so there was a risk of 'contamination' of the control group through behaviour change materials delivered to GPs.

What this meant

The PAAP intervention was safe and effective at increasing penicillin use and reducing total antibiotic use.

Work package 2.2: Health economic evaluation: assessing the consequences of introducing the penicillin allergy assessment pathway intervention into the National Health Service

Aims

The aim was to conduct an economic evaluation of the cost-effectiveness of the PAAP versus usual clinical care (UCC) from the perspective of the NHS and Personal Social Services in England. This was done in two parts: first, on

a within-trial basis using up to 12-month follow-up and, second, using a decision analytic model with a 5-year time horizon. We also assessed whether conducting a new follow-on RCT of PAAP was worth the extra cost.

Results

The mean per patient costs of PAAP were £170 at 12 months. Mean (95% CI) cost differences in the intervention group relative to UCC were: −£11 (−24, 3) for primary care, −£114 (−432, 204) for hospital admissions, £0 (−100, 100) for outpatient attendances and −£13 (−42, 17) for emergency care. Mean total costs were £1301 and £1269 in intervention and UCC group, respectively (difference: unadjusted 32.31, imputed + adjusted 55.61); mean quality-adjusted life-years (QALYs) were 0.866 and 0.830, respectively (difference: unadjusted 0.036; imputed + adjusted 0.0051). The within-trial analysis showed that PAAP was associated with an incremental cost-effectiveness ratio of £10,938 per QALY gained relative to UCC. It generated an incremental net health benefit of 0.0023 QALYs and incremental monetary benefit of £41 (58% probability of cost-effectiveness) per patient, at a threshold of £20,000/QALY and 0.0032 and £92 (64%), respectively, at a threshold of £30,000/QALY. The probability of PAAP being cost-effective varied the most by gender and number of antibiotic prescriptions in the year before trial enrolment.

The decision tree model yielded predictions of both cost savings and QALY benefits with PAAP versus UCC in the long term. The incremental net monetary benefit was 806 (48% probability of cost-effectiveness).

The cost of a new follow-on trial modelled on ALABAMA and involving 1267 participants was estimated to be £2.37 M. The expected value of sample information produced by the new trial from reducing the costs of making the wrong decision based on a 5-year analysis of PAAP costs and benefits is £19.60 M over the adult population in England expected to benefit from PAAP in the next 10 years.

Limitations

Health-related quality-of-life outcomes of trial participants were collected at baseline and at the trial end, which for some participants was < 12 months due to early trial termination due to COVID-19. The economic modelling relied on simplifying assumptions regarding the long-term cost and QALY outcomes due to the limited follow-up period of the trial.

What this meant

Penicillin allergy assessment pathway was likely to be cost-effective, modelling suggested PAAP would be cost-effective, but uncertainty was high. A follow-on trial would be expected to be worthwhile. There is, however, additional considerable uncertainty about long-term costs of AMR which we have not factored in as they are out of the scope of this analysis or perhaps would be related to a future trial.

Work package 2.3: Process evaluation: assessing implementation of the penicillin allergy assessment pathway intervention

Aims

We aimed to explore participants and healthcare professionals' experiences of trial procedures. Specifically, we explored participants and healthcare professionals' views and experiences of PAT, test results and future antibiotic use.

Results

Clinicians and patients' interviews:

General practitioners were motivated to join the trial because they believed it provided clear benefit for patients. Overall, GPs were positive about their experiences of the trial and the *'protocolisation'* which engendered trust in trial procedures and results. They had a sense of shared responsibility of risk. Participants reported feeling safe at the test clinic, empowered and being well looked after. Most participants trusted the test to be accurate and were relieved to have received a negative test that enabled them to take penicillin in the future. Two participants experienced delayed side effects and so despite a negative test result requested to retain their allergy status.

Participant survey

At baseline, participants already believed that penicillin was the best treatment, that it was important to know whether they were truly allergic, that testing was safe and that they were not frightened by a serious reaction. They were also happy to take penicillin in the future if they tested negative. At follow-up, participants reported that they disagreed that they were allergic to penicillin and that there was a high chance they would have a serious reaction during the test. Their responses to the other questions did not change from follow-up.

Limitations

The qualitative interviews and patient survey recruited clinicians and patients from a small number of general practices in England; the results should be interpreted cautiously in terms of their transferability to other settings.

What this meant

The findings reinforced the effectiveness of the behavioural element intervention and emphasised the need to consider all elements of a testing process as well as the behaviours that need to change to ensure patients receive the anticipated benefits of testing. Findings suggest that for a de-labelling pathway to be successful in primary care a safe, accessible and reliable service must be available, and GPs need to be provided with step-by-step guidance to identify low-risk patients.

Trial registration

This clinical trial is registered as Current Controlled Trials ISRCTN20579216 and ClinicalTrials.gov as NCT04108637.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Programme Grants for Applied Research Programme (NIHR award ref: RP-PG-1214-20007) and is published in full in *Programme Grants for Applied Research*; Vol. 14, No. 11. See the NIHR Funding and Awards website for further award information.

Synopsis

Research pathway diagram

The research pathway diagram is presented in *Figure 1*.

Summary of alterations to the programme's original aims/design

On 13 January 2023, the NIHR Research Programme Grants for Applied Research board reviewed trial progress with the research team in relation to the coronavirus disease discovered in 2019 (COVID-19) pandemic and decided not to provide additional funds to compensate for slow recruitment caused by COVID-19. Although a steady rate of recruitment had been achieved during the pandemic, it was not at the rate anticipated pre-COVID-19. The funder recognised the value of the trial but maintained that the financial climate had changed within the context of the UK Department of Health and Social Care's wider 'Research Reset' initiative. As a result of this funding review, a revised primary trial outcome was agreed (16 May 2023). This allowed the team to provide a powered trial with a reduced sample size. NHS Research Ethics Committee (REC) and Health Research Authority approval was granted for the protocol amendment 12 July 2023 and clinical trials registration remained in place.

Summary of the changes to the research:

1. The primary outcome was changed to: The proportion of participants who received prescriptions for a penicillin when attending for predefined conditions where a penicillin is the first-line recommended antibiotic during the course of routine primary care, up to 12 months post randomisation.
2. A new power calculation was carried out: A total sample size of 848 to 656 were estimated to provide a 90% and 80% power, respectively, to detect an increase in the proportion of penicillin prescriptions from 4% (usual care) to 14% [penicillin allergy assessment pathway (PAAP)] over the year after randomisation at 5% level of significance (two-sided) and 10% attrition.
3. The previous primary outcome of treatment response failure became a secondary outcome.
4. Additional secondary outcomes were added to measure penicillin allergy de-labelling and relabelling rates: (a) The proportion of ALABAMA participants whose labels were removed from the electronic health record (EHR) allergy section at 3 months post randomisation and (b) the proportion of these participants' labels that remained removed from the medical EHR allergy section up to 12 months post randomisation.
5. Cost-effectiveness analysis was expanded: Based on a probabilistic Markov model, the value of conducting further research in key uncertain outcomes was added using 'Expected Value of Sample Information'. This analysis was planned to determine whether the costs of conducting further research on uncertain parameters would be 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.
6. The process evaluation (PE) was modified to explore facilitators/barriers to changes in prescribing after negative penicillin allergy status is confirmed. The PE sought to understand how confident participants were about taking penicillin after a negative penicillin allergy test result and interview participants who request their allergy record not be changed.

Background

The importance of antimicrobial resistance (AMR) and the need to reduce its impact is well recognised. One way to reduce AMR is to improve the quality of antibiotic use as well as reduce the quantity of antibiotics used. Penicillins are the most prescribed antibiotics and are first-line therapy for many common infections. Patients with a penicillin allergy label (PAL) are much less likely to be prescribed penicillins[1,2] and may therefore be disadvantaged.

Penicillin allergy records are common affecting about 6% of the UK population.[1] Importantly, fewer than 10% of these patients are truly allergic after allergy assessment.[3] Spurious penicillin allergy records arise for many reasons including

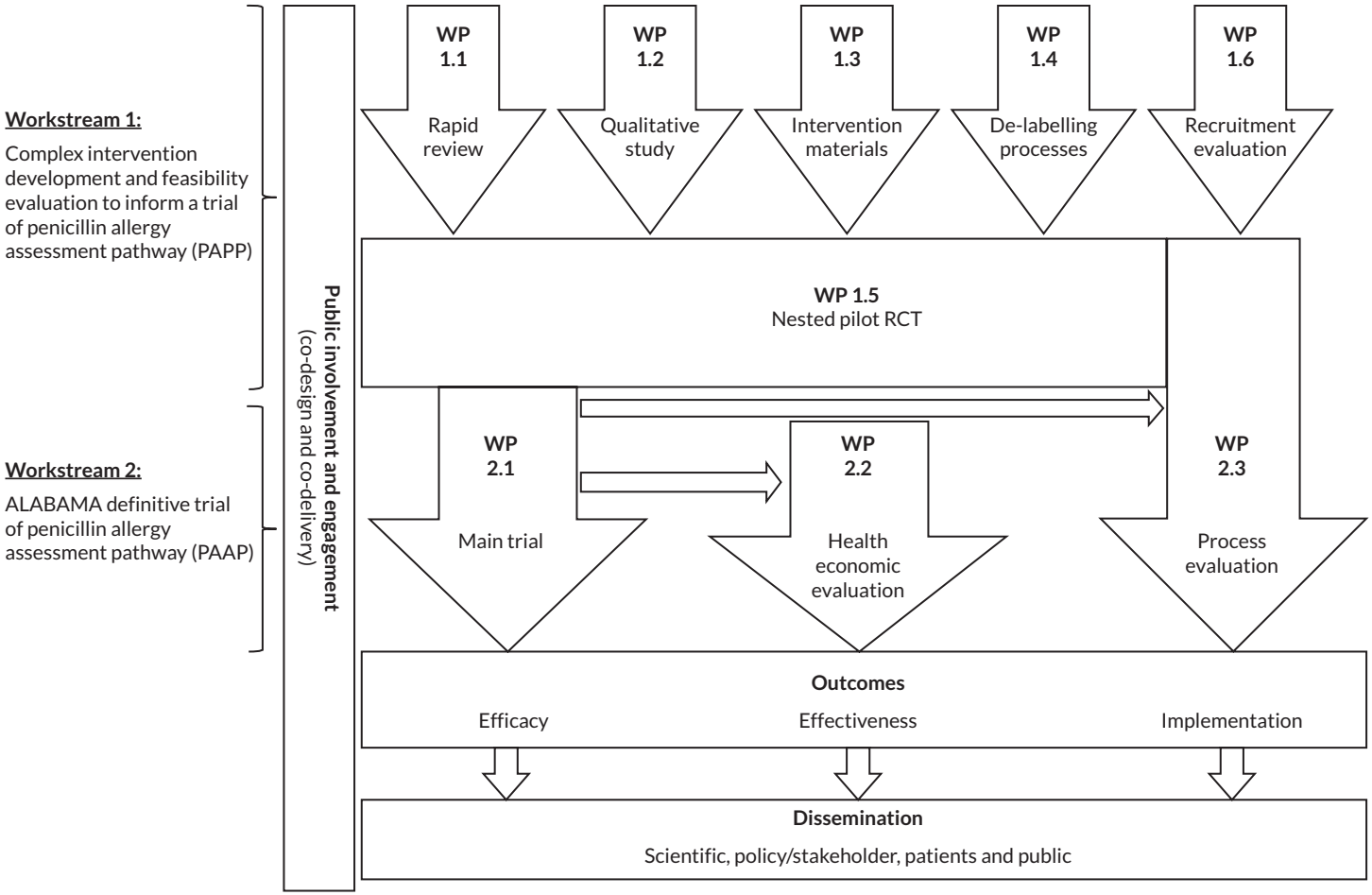

FIGURE 1 Research pathway diagram. RCT, randomised controlled trial; WP, work package.

side effects and symptoms related to the infection requiring antibiotic treatment being mislabelled as allergies; health record systems not easily allowing distinction of allergic symptoms and side effects; and allergy waning over time. Consequently, a significant proportion of the population are restricted access to highly effective penicillins.

Several negative health outcomes have been associated with PALs. Penicillin allergy records are associated with AMR; for example, 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).[1,2,4] This appears to be because patients with a penicillin allergy are usually prescribed alternative antibiotics like fluoroquinolones, macrolides and clindamycin.[2] 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.[1] Systematic review evidence indicates that antibiotic-allergies affect health outcomes, increasing mortality, length of hospital stay and costs.[5] The large discrepancy between reported and true allergy rates suggests that introducing a 'pre-emptive' 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. The focus of ALABAMA was spurious or 'false-positive' penicillin allergy records, and whether a trial of a complex intervention aimed at correcting such records is safe, clinically effective and cost-effective.

Workstream 1: Complex intervention development and feasibility evaluation

Work package 1.1: Rapid review of evidence regarding patient/prescriber views of penicillin allergy and behaviour change in relation to allergy testing and antibiotic prescribing

Aim

To synthesise published evidence of patients' and/or clinicians' views and experiences of penicillin allergy testing (PAT) services and influences on antibiotic prescribing behaviour in the context of penicillin allergy.

Methods

We undertook a rapid review and narrative synthesis of the relevant published literature in health and social science databases. See *Appendix 2*, *Figure 5* for Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram showing the flow of information through the phases of the review. Searches were limited to English language and priority placed on hand-searching relevant reference lists, rather than exhaustive database searching. Relevant databases were searched up to 17 October 2017. The output was a narrative synthesis of the results, informed by the behaviour change literature (see *Appendix 1*, *A1*).

Limitations

Limited numbers of cross-sectional survey studies were identified, assessing clinical aspects of penicillin allergy tests and accuracy. Qualitative studies were not identified. Exploration of patients' and clinicians' motivations and beliefs was generally a secondary aim. Studies therefore provided limited insight into patients' and clinicians' behaviours. A full systematic review might have found more studies. Lack of quality assessment and double-checking could have introduced a bias.

Key findings

Patients' views of PAT revealed their concerns about testing but also some advantages. Uncertainty about referral criteria for PAT was reported by clinicians. After a negative PAT, there remained a reluctance to prescribe and consume penicillins among some clinicians and patients, respectively; lack of confidence in test results and fear of subsequent reactions were drivers. This work was published in *Antibiotics (Basel)*.[6]

Inter-relationship within the programme

This work showed the need for qualitative studies to better understand the influences on clinician and patient uptake of PAT. It suggested that clinicians and patients would need to be supported to engage with PAT services and equipped with the skills to use penicillins appropriately following a negative allergy test result. Literature searches informed topic guides for both qualitative studies [work package (WP) 1.2] and development of intervention materials (WP1.3).

Work package 1.2: Qualitative study of patient/prescriber attitudes to penicillin allergy and penicillin allergy testing

Aims
To identify primary care clinician and patient views on barriers and enablers to PAT and subsequent antibiotic use.

Rationale
Work package 1.1 identified a gap in knowledge about patient/clinician views on penicillin allergy/PAT, and how patients were likely to interpret negative penicillin allergy test results and a subsequent penicillin prescription. In addition, it was not known how a negative test and penicillin allergy status reassigned as negative would impact on general practitioner (GPs') antimicrobial prescribing behaviour.

Method
The literature review (WP1.1) findings were used to inform interview topic guides for patients and prescribers. We drew upon existing models of behaviour by ensuring that topic guides asked about key determinants of behaviour which were likely to influence patient uptake of PAT and prescribing behaviour following the result of PAT. Topic guides were piloted with patient and public involvement and engagement (PPIE) contributors and clinicians.

Semistructured interviews were used, with a purposive sample of GPs who had managed patients with PAT results or had no experience of managing patients undergoing penicillin allergy assessment. Interview questions explored GPs' views of managing patients with penicillin allergy, PAT and associated antimicrobial prescribing.

Semistructured interviews were carried out with a purposive sample of patients identified in immunology clinics, who had penicillin allergy and who had either experienced PAT and tested negative and had the opportunity to experience a change in prescribing; or, not been tested for penicillin allergy. Interview questions explored patients' understanding and beliefs about: penicillin allergy; AMR; impact of a penicillin allergy record on their long-term health; PAT, the testing process (as experienced or hypothetical); and their views on taking penicillin following a change to their allergy status. Interviews were audio recorded, professionally transcribed verbatim and managed with NVivo. Data were analysed using thematic analysis. Please also see *Appendix 1*, *A1.2*.

Limitations
This was a qualitative study with a purposeful sample that recruited from one region in England; the results should be interpreted cautiously in terms of their transferability to other settings.

Key findings
Thirty-one patients were interviewed and 19 GPs. Patients were generally found to be unaware of the benefits of PAT. Where patients had experienced negative consequences of their PAL they were motivated to be tested. Clinicians were reluctant to update patient's penicillin allergy records using their clinical judgement alone. Clinicians had limited experience of referring patients with PALs for assessment and testing processes. Clinicians described numerous potential benefits of testing. Patients who had been tested reported benefits of the process. There was uncertainty about who should ensure the patient understood allergy test results among GPs. This work was published in *The Journal of Allergy and Clinical Immunology: In Practice*[7] and in *BMC Family Practice*.[8]

Inter-relationship within the programme
This was the first qualitative interview study to provide in-depth understanding of patient and clinician views and experiences of PAT and subsequent penicillin use. Previous studies had mainly used survey designs focusing on clinicians' views; this study filled an important gap by providing a patient-centred and clinician-centred perspective. The findings informed the development, design and implementation of intervention materials for patients and prescribers for use in the nested pilot (NP) and main trial (WP1.3).

Work package 1.3: Development of intervention materials to support patient and clinician engagement with penicillin allergy assessment pathway

Aim
To develop intervention materials to support the implementation and uptake of PAAP by clinicians and patients.

Rationale
The implementation of a new PAAP required both clinicians and patients to carry out new behaviours. Key patient behaviours included attending for a penicillin allergy test and taking a penicillin if prescribed after a negative test. At the time of trial design, this typically involved a half day in a specialist allergy clinic in secondary care, undergoing skin tests and, if these were negative, having an oral challenge with a penicillin. Key clinician behaviours include GPs referring patients for a penicillin allergy test, updating medical records with test results, and, following a negative result, prescribing a penicillin for appropriate infections.

Method
We used an integrated approach to intervention development that combined theory-based, evidence-based and person-based approaches. We collated evidence from WP1.1 and WP1.2, PPIE representatives and expert discussions to understand the behaviours of interest in context and to establish guiding principles. We then identified four specific target behaviours and used the Theoretical Domains Framework to determine barriers and facilitators to change, and how intervention components would support the desired behaviour change based on evidence identified in WP1.1 and WP1.2. The intervention components were also mapped onto Behaviour Change Wheel including behaviour change techniques. Once drafted, materials were trialled for their acceptability with patients and clinicians and their feasibility for use in general practice using 'think-aloud' interviews. Think-aloud interviews involved patients looking at, reading/watching and commenting on materials as they would view them in real life. Small numbers of patients were needed to make sure the information is easily understandable and usable. Please also see *Appendix 1*, *A1.3*.

Limitations
A limitation of the ALABAMA intervention package is uncertainty about its wider application outside the trial. Allergy services across the UK vary significantly, and access to specialist testing ranges widely. Cohesive action across the health system will be necessary to successfully widen access to penicillin allergy assessment. Our dissemination activities involve engagement with stakeholders across the health system [e.g. NHS England, UK Health Security Agency, National Institute for Health and Care Excellence (NICE)] to develop an NHS implementation plan. The intervention will be centred around functionality within SystmOne (an electronic medical record system widely used in general practice), but the intervention package developed within ALABAMA will need to be modified to allow full functionality in other GP EHRs systems to optimise knowledge mobilisation.

Key findings
Key intervention behaviours were identified as GP referring for allergy testing, patient attending testing, GP prescribing after a negative allergy test and the patient consuming penicillin after a negative test. To support clinicians and patients in undertaking the desired behaviours involved in the PAAP, materials were developed that were intended to increase knowledge of PAT, support beliefs about the importance of testing and the importance of increase confidence in performing the behaviours safely by providing a supportive environment. Materials comprised separate information booklets for GPs and patients, EHR pop-ups, post testing result cards for patients, trial work instructions and training material, patient and clinician letters. Feedback from think-aloud interviews identified changes required to draft intervention materials to increase acceptability and feasibility of the PAAP with patients and clinicians. This work was published in *BMJ Open*.[9] https://doi.org/10.1136/bmjopen-2019-035793

Inter-relationship within the programme
The resources relating to the intervention booklets were printed and given to participating GPs and to participants randomised to the intervention group during the NP and main trial. For further knowledge mobilisation from ALABAMA to NHS implementation, further stakeholder engagement has been identified and processes are being explored to expand the functionality developed within SystmOne to other GP EHR systems, required to optimise patient identification and updating of health records when the penicillin allergy assessments are reported.

Work package 1.4: Design of systems and processes for recording/updating penicillin allergy records

Aim
To determine how best to update penicillin allergy records to maximise the impact of PAT while maintaining patient safety.

Rationale
It was known that primary care EHRs were often not updated following routine inpatient penicillin allergy assessment. Without an update to records, it is unlikely that the intervention would impact on antibiotic prescribing and health outcomes.

Methods
Qualitative research undertaken in WP1.2 and WP1.3 helped to inform this work package. GP interviews and structured consultation meetings with stakeholders [comprising The Phoenix Partnership (TPP) representatives, clinical co-applicants, GPs, prescribers, patient representatives]. Current methods of recording and removing penicillin allergy records in SystmOne were mapped. The pros and cons of these processes documented, and any patient safety concerns discussed. Discussions focussed on the feasibility of introducing changes to the way in which penicillin allergy test results were recorded within available resources and systems, to ensure maximum transfer across patients' EHRs. Further consultations were held with senior TPP representatives and GP advisors after the pilot trial and modifications made to processes. Please also see *Appendix 1*, *A1.4*.

Limitations
The processes that were developed were specific to SystmOne and equivalent functions would need to be established for other EHR providers.

Key findings
Qualitative interview research found GPs were happy to update medical records after a negative test result provided there were directions. GPs also expressed concerns about patients becoming relabelled as penicillin allergic. It was found that a penicillin allergy record in SystmOne could be removed in one of two ways: 'ended' or 'marked in error'. The former continued to generate alerts when GPs tried to prescribe penicillins, whereas the latter maintained an audit trail, but the penicillin allergy alert was removed. After consultation with TPP and GPs, it was decided that 'marking the record in error' was the safest and most appropriate method to update records if a patient had a negative penicillin allergy test result. GP trial training and standard operating procedures were developed to inform GPs how to update records. Results records were developed to include template functions in SystmOne. Processes were developed to also update secondary care records in line with primary care results. The NP showed that de-labelling occurred for 11/14 (79%) patients but 4 records were 'ended' rather than marked in error. To improve on this a new function in SystmOne was utilised to send a 'task' to the GP. This work has been published in *BMC Trials*.[10]

Inter-relationship within the programme
The functionality developed in SystmOne to allow identification of potentially suitable patients for PAAP, and also de-labelling processes to allow updates within the EHRs, developed in this work package were incorporated successfully into the ALABAMA NP and definitive trial. These processes will need to be reproduced across other GP EHR systems, beyond just SystmOne, to facilitate wider NHS implementation.

Work package 1.5: Assessment of the feasibility of delivering a randomised controlled trial of the penicillin allergy assessment pathway intervention versus usual clinical care

Aim
To undertake a NP randomised controlled trial (RCT) with feasibility outcomes to assess safety, acceptability and practicality of delivering a trial of the PAAP intervention.

Rationale
The original objectives are presented below but had to be modified due to COVID-19 and the necessary pause in recruitment and testing:

- establish progression criteria from NP to main trial with the TSC
- assess performance of electronic identification of suitable patients from EHR
- assess willingness of GPs to refer to PAAP and participants to undergo testing

- determine optimal PAAP safety monitoring strategy
- establish the preferred participant flow from recruitment to PAAP
- describe prescriber's responses to changes in penicillin allergy records
- assess effectiveness of research nurse telephone follow-up/data capture
- effectiveness/logistics of participant symptom diary completion
- re-prescription rates and duration of symptoms rated 'moderately bad or worse'
- operation of recruitment across two regional localities (Leeds/Bradford)
- confirmation of estimates of antibiotic prescribing frequency/treatment response failures.

Methods

Please also see *Appendix 1*, *A1.5*. A NP RCT with feasibility outcomes. The plan was to recruit 8 GP sites over 3 months; each site recruiting 12 participants, 96 in total. GPs confirmed suitability of patients identified from a report generated in the SystmOne EHR system. Eligible and willing patients were then consented and randomised to either PAAP or UCC.

Limitations

Onset of the COVID-19 pandemic delayed randomisation and testing for some consented participants. COVID-19 interrupted follow-up for only a minority, meaning the planned monthly telephone calls did not occur for one participant. Many patients actively avoided contacting GPs during the pandemic meaning that antibiotic prescribing fell during this period, potentially reducing the number of primary events. Primary events were antibiotic prescriptions for a pre-defined list of infections which prompted the participant to complete a symptom diary for trial outcome data analysis.

Key findings

Progression criteria to main trial

The NP trial (with feasibility outcomes) had a recruitment target of $n = 96$ consented participants by end of April 2020. The Stop/Go criteria agreed by the TSC were for automatic 'go' if recruitment achieved > 80% (i.e. $n = 76$) of the target. Before having to pause trial activities in April 2020, due to COVID-19 and redeployment of ALABAMA trial staff, 81 participants were consented (*Figure 2*).

As > 80% recruitment was achieved by the progression criteria census date, the independent Data Monitoring and Ethics Committee (DMEC) and TSC recommended automatic progression to main trial to be actioned once the COVID-19 restrictions were relaxed. The ALABAMA trial was granted approval on 4 June 2020 to restart as part of The Leeds Teaching Hospitals NHS Trust local prioritisation using the NIHR CRN RE-START Framework with proposed re-start timeline of a 1 November 2020 and approval to advertise for additional clinical delivery staff.

Electronic identification of patients

Electronic identification of suitable patients from GP EHR was successful and development is detailed in *BMC Trials*.[10] Overall, the search identified 1.5% of the total general practice population as potentially suitable (*Table 1*).

Willingness of GPs to join the trial and refer participants

The number of general practices/week enrolled into the trial is shown in *Figure 3*. Willingness of GPs to refer patients to PAAP was demonstrated by an overall invitation rate of 62.7% of potentially eligible patients (see *Table 1*).

Willingness of participants to undergo testing

Willingness of participants to undergo testing was demonstrated by 14 of the 38 randomised participants undergoing testing. Number patients/practice/month enrolled into the trial (see *Table 1*).

Determine optimal penicillin allergy assessment pathway safety monitoring strategy

The DMEC reviewed safety data on completion of the NP trial and concluded it was safe to continue to main trial. It was decided to monitor safety of PAT at days 2–4 and days 28–30 after testing.

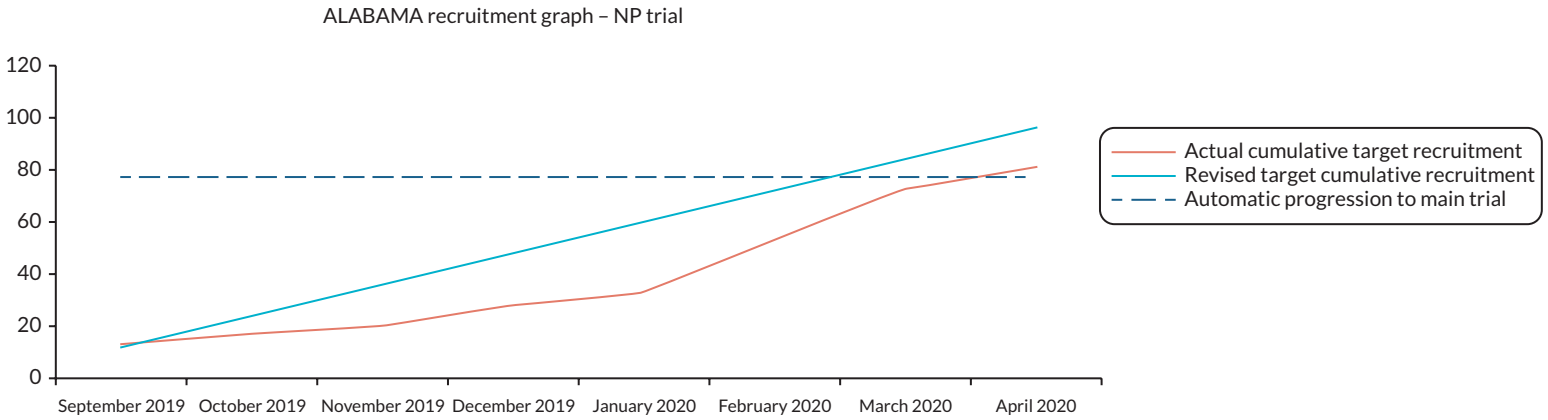

FIGURE 2 ALABAMA NP trial recruitment graph.

TABLE 1 Summary of ALABAMA NP trial recruitment by GP practices

Practice ID	GP practice list size	No. of patients appeared on S1 search list	No. of patients received invitation	Total no. of expression of interests	Total no. of patients consented	No. of patients randomised
1 NP Practice	11,417	141	141	20	5	5
2 NP Practice	10,990	106	72	7	6	3
3 NP Practice	5715	51	35	10	3	1
4 NP Practice	8582	277	199	29	20	13
5 NP Practice	6898	104	72	18	8	4
6 NP Practice	6238	108	54	6	3	0
7 NP Practice	7031	80	61	2	0	0
8 NP Practice	13,724	251	88	11	8	4
9 NP Practice	10,404	174	106	19	12	3
10 NP Practice	4900	75	43	14	11	3
11 NP Practice	8700	139	73	14	5	2
12 NP Practice						
Total (*n*)	94,599	1506	944	150	81	38 (43 awaiting randomisation)
% of previous column		1.5	62.7	15.8	54	46.9

Establish the preferred participant flow from recruitment to penicillin allergy assessment pathway

The processes of setting up a data-secure 'ALABAMA unit' within the SystmOne EHR system, referring participants into the unit, allocating to treatment group, and follow-up via the ALABAMA unit are described in methodology paper 'Embedding randomised trials of complex interventions in primary care clinical records: demonstrated by using SystmOne electronic health records to deliver the ALABAMA RCT of penicillin allergy assessment'.[10]

Describe prescribers' responses to changes in penicillin allergy records

See WP2.3 PE.

Assess effectiveness of research nurse telephone follow-up/data capture

Six of the 38 (15.8%) participants had a primary event, or multiple primary events, on the clinical trial database prior to April 2020; 7 primary events were recorded in total. All of these primary events were followed up by phone call at days 2–4 and 85.7% had a 28- to 30-day follow-up call. Fifteen of the 38 (39.5%) participants had PAT, 100% of these were followed up by phone call at days 2–4 and 66.7% at days 28–30 (by the end of April 2020).

Effectiveness/logistics of participant symptom diary completion

Of the seven primary events, two symptom diaries were completed. The symptom diary completion rate was therefore 33.3% at this point (symptom diary completion was only required for the first primary event). Given low diary completion rates, it was clear that the 38–30 follow-up call would be needed to ensure 'treatment response failure' data could be captured.

Re-prescription rates and duration of symptoms rated 'moderately bad or worse'

Two of the seven (28.6%) primary events needed a re-prescription and the mean average symptom duration (before patient indicated this as resolved) was 5.6 days. This information was extracted from the symptom diaries and data from the 28- to 30-day follow-up.

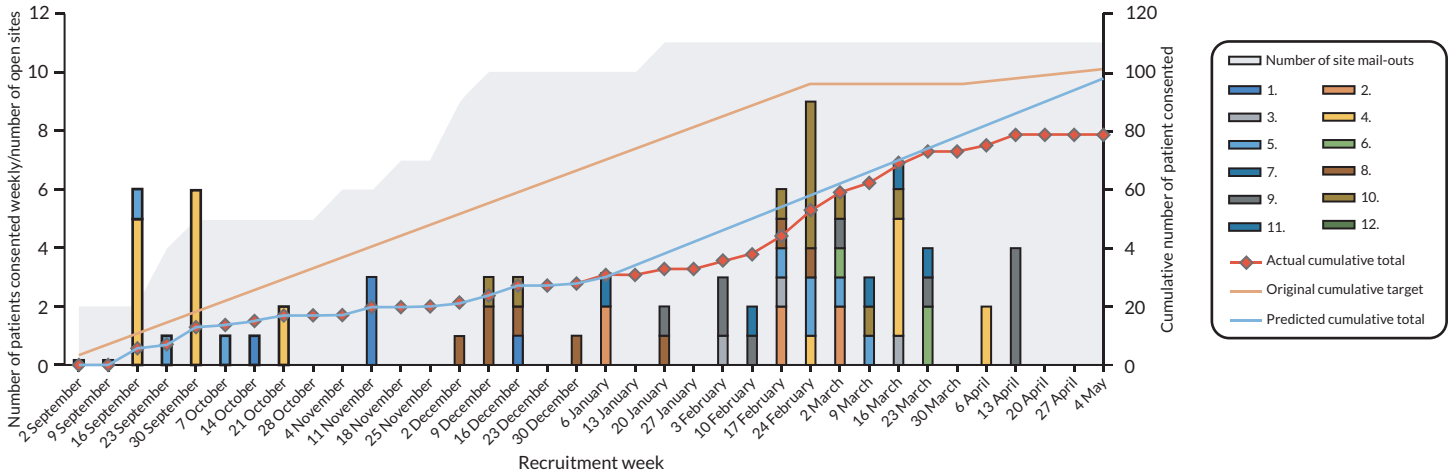

FIGURE 3 ALABAMA NP recruitment graph by week (2 September 2019–4 May 2020) and GP practice. Coloured vertical bars represent general practices.

Operation of recruitment across two regional localities
This was not assessed until the main trial.

Confirmation of estimates of antibiotic prescribing frequency/treatment response failures
There were 7 primary events for the 38 NP trial participants by April 2020. However, the participant follow-up period ranged from <1 month to 6 months at this point. These data were reviewed by the DMEC, who granted permission to continue with estimated sample calculation.

Inter-relationship within the programme
Findings from the NP trial informed methods of screening and follow-up and further informed the implementation of intervention materials in the main trial. Satisfaction of Stop/Go criteria meant the main trial could commence once approval had been given and adjustments made to ensure participant safety in the context of COVID-19. Following a performance evaluation of the screening report to identify potentially eligible patients, the period during which a prior antibiotic treatment was allowed was increased to 24 months. This increased the eligibility to 2.75% of general practice population in the main trial. Some inclusion and exclusion criteria were modified for and during the main trial. Low rates of diary completion highlighted the importance of the days 28–30 follow-up call in the main trial.

For de-labelling processes, please see WP1.4. Recruitment changes are reported in WP1.6.

Work package 1.6: Understanding recruitment to the ALABAMA penicillin allergy assessment pathway trial

Aims
To optimise recruitment to the trial and understand why patients wanted to participate in the trial

Methods
Regular review of recruitment data was used to inform this WP. During the NP trial, the percentage of patients who expressed an interest after being invited was monitored as was the percentage of patients invited who consented to participate. In weekly team meetings and trial management group meetings, ways to improve recruitment were discussed and agreed by team consensus. The original plan for general practice staff to record the patient information sessions when patients provided consent was dismissed as impractical. Instead of this. Semistructured interviews with participants carried out as part of the PE provided some insights into people's motivation to take part in the trial.[11] Where patients provided information about declining participation, this was recorded by research nurses (see *Appendix 1*).

Limitations
Formal analysis of the different approaches used to improve recruitment was not undertaken; rather an iterative consensus process was used.

Key findings
Initially there were low rates of conversion from expression of interest to consent. During the NP trial, the following measures were approved and implemented to maximise recruitment:

- NHS research staff were seconded to the local GP confederation enabling research nurses to work as part of the general practice team and follow up non-responders/pre-consented participants with reminders on behalf of the GP.
- Verbal telephone consent, which saved GP/participants' time.
- Non-responder letters were sent to patients who did not respond to the first mail-out.
- Up to two follow-up calls could be made to non-responders by Research Nurses to find out if the participant has received the ALABAMA trial information pack from their GP, share information with the patient on why the trial is important and to collect the reason for not taking part (if willing).
- Posters for display in GP practices and local pharmacies, to help create awareness and increase recruitment.

- Non-responder follow-up (via mail or telephone) had a noticeable positive impact on response rates. Forty phone calls were made: 32.5% (*n* = 13) were not interested but no specific reason given, 15% (*n* = 6) were not aware that they had a PAL, 10% (*n* = 4) declined due to other (work) commitments, 10% (*n* = 4) declined due to their age, 7.5% (*n* = 3) declined due to comorbidities, 7.5% (*n* = 3) declined due to COVID-19, 5% (*n* = 2) declined due to recent bereavement, 5% (*n* = 2) declined due to caring commitments, 5% (*n* = 2) declined due to anxiety of being tested, 2.5% (*n* = 1) declined due to pregnancy.
- As part of our recruitment strategy for the main trial, we recruited additional sites: South Yorkshire and Cornwall.

Inter-relationship within the programme

The findings in relation to methods of recruitment and communication with patients were used in the main trial.

Workstream 2: ALABAMA definitive trial of a penicillin allergy assessment pathway

Work package 2.1: Randomised controlled trial of the safety and clinical effectiveness of the penicillin allergy assessment pathway intervention versus usual clinical care on antibiotic prescribing and health outcomes

Aim

To determine whether a pre-emptive (carried out in advance of need) PAAP intervention is safe and clinically effective in improving antibiotic prescribing and patient health outcomes in patients with a record of penicillin allergy in their primary care EHRs.

Method

See *Appendix 1*, *A2.1*, published protocol[12] and protocol amendment.[13] In brief, this was a pragmatic, open-label, multi-centre, individually randomised, controlled trial of pre-emptive PAAP versus UCC. The PAAP intervention comprised identification of patients most likely to benefit; eligibility check; consent; allergy and antibiotic history; penicillin allergy test in hospital setting (oral challenge test with or without prior skin testing); communication of results to GP; updating of records and behaviour change materials. The primary outcome was receipt of a penicillin during the 1-year follow-up period. Secondary outcomes were mortality, hospital admission and length of stay, antibiotic use, treatment response failure, duration of symptoms, de-labelling rates, and MRSA and *Clostridioides difficile* infection (CDI).

Limitations

The trial took place during the COVID-19 pandemic which impacted on recruitment. The primary outcome had to be changed from treatment response failure to penicillin prescribing. In addition, the trial may underestimate the effect of the intervention as visits to GPs and antibiotic prescribing were both reduced during the COVID-19 pandemic. The trial was open label so there was a risk of 'contamination' of the control group through behaviour change materials delivered to GPs.

Key findings

Eight hundred and twenty-three participants were randomised, 411 to PAAP and 412 to UCC (12 participants were subsequently withdrawn). Recruitment progress versus target is outlined in *Figure 4*. The Consolidated Standards of Reporting Trials diagram can be found in *Appendix 3*, *Figure 6*.

Penicillin allergy assessment pathway resulted in a statistically significant increase in penicillin allergy de-labelling at 12 months [321 de-labelled in PAAP group vs. 2 in UCC group; risk difference 87.4% (84.1 to 90.9), *p*-value < 0.0001] and penicillin prescribing [72 in PAAP group vs. 14 in UCC group; adjusted relative risk 5.26, 95% confidence interval (CI) 3.03 to 9.18]. Total defined daily dose were reduced (adjusted median difference −3.17, 95% CI −6.11 to −0.23). Prescriptions of non-penicillin antibiotics reduced in the PAAP group compared to the UCC group. There were no important differences in safety outcomes. The PAAP intervention did not significantly affect mortality, hospital admissions or hospital length of stay, duration of symptoms, MRSA or CDI rates, or treatment response failure rates. PAAP intervention significantly increased de-labelling at 3 and 12 months. This work has been published in *Lancet Primary Care*.[14]

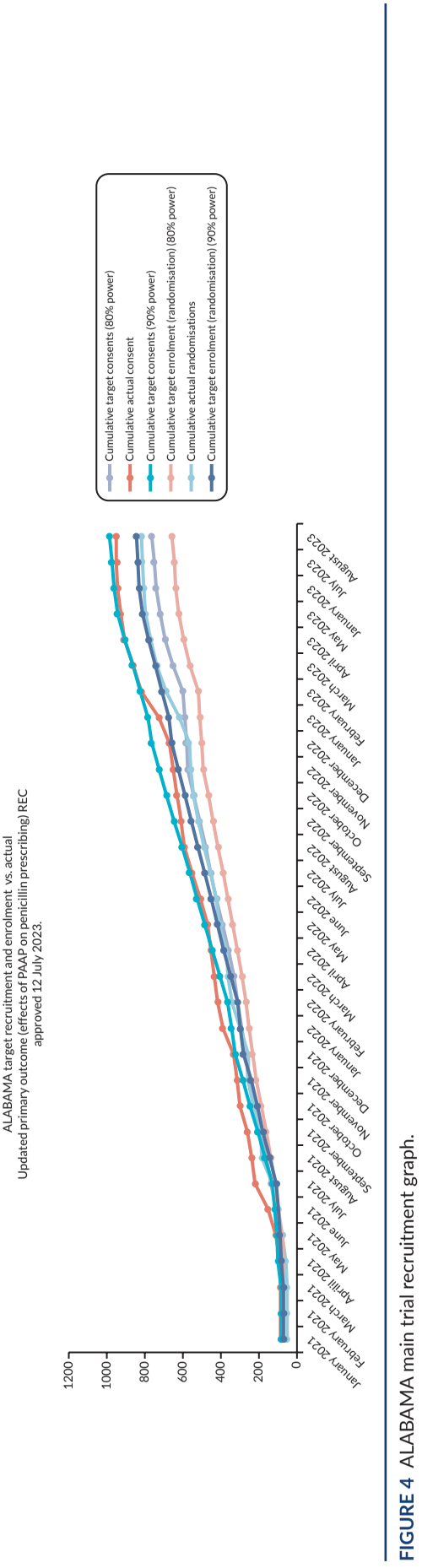

FIGURE 4 ALABAMA main trial recruitment graph.

Inter-relationship within the programme

Prior work packages came together to allow delivery of a successful multicentre trial with a positive outcome in spite of setbacks caused by the COVID-19 pandemic. The findings are clinically important as the intervention allowed more participants to receive first-line therapy and reduced overall antibiotic consumption, which could help to reduce the selection pressure for AMR if implemented more widely. The findings will be disseminated to patients and the general public and communicated to policy-makers and key stakeholders in a series of events aimed at widening access to penicillin allergy assessment and resolving unanswered questions through further research.

Work package 2.2: Health economic evaluation: assessing the consequences of introducing the penicillin allergy assessment pathway intervention into the National Health Service

Aims

The aim was to conduct an economic evaluation of the cost-effectiveness of the PAAP intervention, versus UCC from the perspective of the NHS and Personal Social Services in England. This was done in two parts: first, on a within-trial basis using up to 12 months of follow-up and, second, using a decision analytic model with a 5-year time horizon. Due to the early termination of the ALABAMA trial, we also sought to assess whether conducting a new follow-on RCT of PAAP was worth the extra cost.

Methods

We followed the NICE's reference case. We employed a cost–utility approach, with benefits measured in terms of quality-adjusted life-years (QALYs) using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) measure and crosswalk recommended by NICE. We estimated costs of the PAAP intervention from trial procedures, informed by findings from our systematic literature review of costs of penicillin allergy de-labelling.[15] We used individual participant data collected during the trial; primary and/or care EHR data for GP and nurse consultations, and antibiotic prescriptions; Hospital Episode Statistics for inpatient admissions, outpatient and emergency department attendance data; and Office of National Statistics for civic registrations of death. The within-trial analysis used a mixed effects model for costs and for QALYs, controlling for variables and employing multiple imputation of missing data through kernel nearest neighbour predictive mean matching. A full specification of this is available in the supplementary material to our *Lancet Primary Care* publication.[14] A decision tree model, populated with ALABAMA trial data and supplementary information from the findings of the systematic review of costs associated with PAL de-labelling was developed to evaluate the long-term cost-effectiveness of PAAP versus UCC. The decision tree represented the pathway followed by participants within the 12-month trial in terms of the occurrence of PAT, de-labelling and antibiotic treatment failure and, in addition to their within-trial accrued costs and QALYs, included projected annual costs and QALYs (discounted at an annual rate of 3.5%) for four additional years after the trial end. The 5-year time horizon was chosen to align with the longest follow-up for which relevant resource data are available in the literature. Projected annual costs were a function of 12-month penicillin allergy status and treatment failure occurrence as determined from predicted values of regression models fitted to post 12-month individual trial participant data on counts (Poisson regression) for each resource use category (number of hospital admissions, outpatient attendances, emergency care visits, primary care visits and number of prescribed medications) and the corresponding average unit cost per count (ordinary least squares). Due to the lack of utility data after 12 months, QALYs were assumed to remain constant at the observed within-trial values over the 5-year model horizon. While the relabelling rate was negligible in ALABAMA, we investigated an alternative scenario where de-labelled patients would be re-labelled at rates published in the literature within a Markov-chain model structure. We estimated incremental cost-effectiveness ratios (ICER), and net benefit measures at willingness to pay values of £20,000 and £30,000 per QALY. Cost figures are presented in Great British Pounds at prices of 2022–3. The value of conducting a new trial to detect a clinically important difference in treatment failure, the original primary outcome of ALABAMA, was estimated by the difference in the expected value of sample information for the adult population in England expected to benefit from PAAP in the next 10 years minus the costs of the new trial.

Key findings

The mean per-patient costs of the PAAP intervention were £170 (n = 401, intention-to-treat population). At 12 months, mean (95% CI) cost differences in the intervention group relative to UCC were: −11 (−24, 3) for primary care, −114 (−432, 204) for hospital admissions, 0 (−100, 100) for outpatient attendances and −13 (−42, 17) for emergency care. Mean total costs were 1301 and 1269 in intervention and control group respectively (difference: unadjusted

32.31, imputed + adjusted 55.61); mean QALYs were 0.866 and 0.830, respectively (difference: unadjusted 0.036; imputed + adjusted 0.0051). The within-trial imputed analysis (n = 811) showed that PAAP was associated with an ICER of £10,938 per QALY gained relative to UCC. It generated an incremental net health benefit of 0.0023 QALYs and incremental monetary benefit of £41 (58% probability of cost-effectiveness) per patient at a threshold of £20,000/QALY and 0.0032 and £92 (64%), respectively, at a threshold of £30,000/QALY. In sensitivity analyses employing different statistical models, including a gamma distribution with log link, all ICER point estimates were below £20,000 and had a probability of cost-effectiveness > 50%, except for the £46,584 result obtained in the 'as treated' analysis. The probability of PAAP being cost-effective varied the most between gender (86% females vs. 16% males) and number of antibiotic medications in the year before trial enrolment (68% two or more vs. 35% < 2) subgroups.

The decision tree model produced cost savings of £83 and 0.036 more QALYs per patient with PAAP versus UCC in the long term. The incremental net monetary benefit (probability of cost-effectiveness) is 806 (48%). Similar results were found in sensitivity analyses around intervention costs based on different PAAP delivery modes and modifying the model to allow for penicillin allergy relabelling.

The cost of a new follow-on trial modelled on ALABAMA and involving 1267 participants was estimated to be £2,373,856. The expected value of sample information generated by the new trial from reducing the costs of making the wrong decision based on a 5-year analysis of PAAP costs and benefits was £19.59M. This work has been published in *BMJ Open*.[16]

Limitations

Health-related quality-of-life outcomes of trial participants were collected at baseline and at the trial end, which for many participants was < 12 months due to early trial termination. The economic modelling relied on simplifying assumptions regarding the long-term cost and QALY outcomes due to the limited follow-up period of the trial.

Inter-relationship with the programme

The choice of data sources and inputs were aligned with and were informed by the sources, findings and methods of the statistical analysis plan and trial development work for ALABAMA. The findings will contribute to decisions about implementation of penicillin allergy assessment in the wider NHS and on further research. For example, results may be used to justify targeting the intervention to female patients or those who have received two or more antibiotic medications in the last 12 months under current demand and capacity constraints.

Work package 2.3: Process evaluation: assessing implementation of the penicillin allergy assessment pathway intervention

Aims

We aimed to explore patients' and healthcare professionals' experiences of trial procedures. Specifically, we explored patients' and healthcare professionals' views and experiences of PAT, test results and future antibiotic use.

Rationale

Process evaluation is vital for exploring what influenced the delivery and implementation of the complex behavioural intervention (PAAP). This is particularly important in trials of complex interventions in 'real-world' organisational settings such as the NHS.

Methods

Semistructured interviews with patients and healthcare professionals were carried out. Findings from the literature review (WP1.1) and previous qualitative studies (WP1.2, WP1.3) informed the interview topic guides for patients and healthcare professionals. Topic guides centred around views of taking part in the trial. The topic guide for patients included questions around allergy history, impact of their allergy status on their care, motivations to take part in the trial, experience of being part of the trial, experience of PAT, feelings about the test result, intentions or experiences of taking penicillin when needed in the future (when tested negative). The topic guide for healthcare professionals centred on patients' views on referring patients for testing, testing processes, de-labelling, prescribing penicillin to de-labelled

patients and intervention processes and materials. All interviews were audio recorded, professionally transcribed verbatim and managed with NVivo. Data were analysed using inductive thematic analysis.

A survey was sent to all participants who took part in the trial at baseline. Additionally, participants in the PAAP group completed a follow-up survey 28–30 days post randomisation. The survey included 13 items on a 7-point Likert scale (1 = strongly agree, 7 = strongly disagree). Participants were asked about their beliefs around penicillin allergy, their penicillin allergy status, safety and accuracy of the test, and their intentions of taking penicillin in the future in case of a negative test result.

Limitations

The qualitative interviews and patient survey recruited clinicians and patients from a small number of general practices in England; the results should be interpreted cautiously in terms of their transferability to other settings.

Key findings

Clinicians and patients' interviews

Fifty-four healthcare professionals involved in the trial were invited to participate, 18 consented and completed an interview (13 GPs, 3 nurses, 2 pharmacists). We invited 40 trial participants and completed 28 interviews. Out of the 28 participants, 2 received a positive PAT result and 26 received a negative PAT result of these, 24 accepted and 2 declined de-labelling.

General practitioners were motivated to join the trial because they believed it provided 'clear and obvious benefit to patients' and offered a pathway to confirm their patients' penicillin allergy status that would otherwise be unavailable. Overall, GPs were positive about their experiences of the trial and were unequivocal in their praise of the support they received from the trial team, 'it was a perfect study for me, that there was [sic] loads of support'. Additionally, GPs and other participating healthcare professionals commended the *'protocolisation'* of the trial which engendered trust in trial procedures and results. Critically, this also contributed to a sense of shared responsibility of risk. While all GPs had de-labelled patients as part of the trial, only a minority had consulted with a patient post-test and so most had not had cause to prescribe antibiotics. This work has been published in the *British Journal of General Practice Open*.[17]

Patients reported feeling safe at the test clinic and were well looked after by the healthcare professionals administering the test, 'I wasn't sort of left exposed in an unsafe environment'. Most patients trusted the test to be accurate and were relieved to have received a negative test that enabled them to take penicillin in the future. Most patients already questioned their allergy status and were not expecting to have any severe allergic reactions during the test at the clinic and at home. This contributed to their overall sense of safety in taking part to the trial. They also valued the personalised and personable care they received by the team at the testing clinic who made them feel empowered about the test and penicillin allergy reactions in general. Two patients experienced delayed side effects and so despite a negative test result requested to retain their allergy status. Some patients expressed a preference for their general practice to confirm their medical record had been updated (i.e. de-labelled). This work has been published in the *British Journal of General Practice Open*.[11]

Patient survey

All participants completed the questionnaire at baseline (100% response). Three hundred and thirty-four (83%) patients from the PAAP group completed the follow-up survey (all PAT negative).

At baseline patients agreed that penicillin was the best treatment [median interquartile range = 2 (1–3)] and that it was important to know whether they were truly allergic [median = 1 (1–2)]. Respondents agreed that testing was safe [median = 2 (1–2)]. Patients indicated they would be happy to take penicillin in the future if they tested negative [median = 1 (1–2)].

There was variation in whether patients believed they were allergic to penicillin. Many patients were unsure [median = 4 (2–4)]. Patients were also unsure whether there was a high chance of having a serious allergic reaction if they had an allergy test [median = 4 (4–6)]. Generally, patients were not concerned about having a potential serious reaction if they had PAT [median = 5 (3–6)].

At follow-up, after testing negative, patients disagreed with the statement 'I am allergic to penicillin' [median = 6 (6–7)] and disagreed that they would have a serious reaction during a test [median = 6 (6–7)]. Their responses to the other items did not change significantly from baseline.

Inter-relationship within the programme

This work highlights key issues that need to be considered in planning wider access to PAT. These studies demonstrate that GPs would be willing to refer patients for formal allergy testing if the service was available. Findings suggest that for a de-labelling pathway to be successful in primary care a safe, accessible, and reliable service must be available, and GPs need to be provided with step-by-step guidance to identify low-risk patients. Specifically, GPs must feel supported in sharing the risks associated with de-labelling, with secondary care, for them to be prepared to deliver such a programme. Patients require clear and consistent messaging from both primary and secondary care when they have a negative allergy test result and need to be reassured and confident about the difference between an allergic reaction and a side effect of medication.

Involvement of patients and/or the public

How patients and the public have been actively involved to benefit ALABAMA:

Antimicrobial resistance, infection and antimicrobial allergy lack patient groups/hospital networks/local charities to draw upon for PPIE. We established a small bespoke ALABAMA-PPIE-Allergy Forum (PPIE-AF) to contribute to ALABAMA's research design, execution and dissemination strategy.

ALABAMA-PPIE-AF was led by people with self-reported (unsubstantiated) penicillin allergy (Jenny Boards) and those with additional multiple long-term conditions (Rose Woollard, who lived with penicillin allergy for > 60 years) alongside other PPIE public contributors drawn from the established SMILE AIDER PPI Forum, University of Leeds and linking to the NIHR Clinical Research Network (CRN)-led Ethnic Minority Research Inclusion Group. Collectively they have ensured a patient-centred approach, considerate of good principles of equality, diversity and inclusion in study design and delivery.

The ALABAMA PPIE-AF have supported co-design of recruitment strategies, contributed to design of the qualitative enquiry and ethics submission, bringing lived experience to shape the interview topic guide. They highlighted common misconceptions – for example patients may consider they are getting 'better antibiotics' when penicillins are avoided. They guided the need to develop educational material to support patients if their penicillin allergy status is changed. ALABAMA-PPIE-AF ensured the trial material is understandable and appropriate for patients considering participation and that the trial is not too onerous and has a clear patient-centred-approach. Specifically, that ALABAMA's inclusion criteria was broad and included participants that are high antimicrobial users, did not exclude those with multiple long-term conditions, the elderly, nor those from underserved communities. A Bradford test site was opened to facilitate improved access to research within underserved communities where participants wanted local access to testing. Recruitment was encouraged from GPs in areas of deprivation. ALABAMA was mindful to address the shortage of specialist drug allergy services for PAT. As a consequence, PPIE contributors supported PAAP as a shorter, safer testing process using an efficient, innovative 'one stop-service'.

ALABAMA has successful integrated PPIE within our research activities. Jenny and Rose being our main contributors have facilitated the ease of this. Following the AMR-related death of Rose, Jenny has continued as the ALABAMA-PPIE lead. It is timely that PPIE contributors expand now for the dissemination stage. This allows our dissemination strategy to be considerate of people with multiple long-term conditions, a subset likely to benefit in a cost-effective manner and health outcome from PAT. To achieve successful implementation, they will guide the story boards of planned animation and theatre work to improve reach to those most at need by raising awareness of the value of PAT and the importance of participating in clinical trials.

More recently, Dr Shadia Ahmad (ALABAMA Clinical Research Fellow) working with Prof Pavitt has widened our PPIE to establish an AMR and Infection PPIE Group that will now ensure a legacy of PPIE working across several studies, and they are also contributing to the ALABAMA dissemination strategy.

Reflections on what was and what was not successful in the programme

What was successful?

Teamwork

The ALABAMA team worked consistently well together to deliver a powered trial, sometimes under very challenging circumstances. The team has supported each other through periods of ill health and personal loss, keeping the programme going with remarkable dedication and loyalty. Trusting and lasting strong effective research collaborations across organisations have been forged over the 10-year period since the planning of the programme application started.

Trial design and delivery

The collaboration with The TPP and utilisation of functionality within SystmOne EHR system was very successful, allowing for streamlined identification of potential participants and much more efficient trial delivery. It has also paved the way for entirely remote participant follow-up in pragmatic trials. Utilisation of the 'task' function in SystmOne is probably responsible for the high rate of de-labelling seen in participant records in the trial.

In NHS REC substantial amendment SA04 (2020), telephone consent was added as an option for trial recruitment. This was well received by participants who were given the option of telephone or face-to-face consent and usually opted for telephone consent. Research staff also favoured this approach, which enabled recruitment to continue despite restrictions resulting from COVID-19.

Approval was granted (SA04) for follow-up of non-responders after they had received an initial trial information pack by post. This included a follow-on reminder letter or text. These measures were considered to be efficient and helpful.

National Health Service hospital trust-based research staff were seconded to the local GP confederation, enabling research nurses to work as part of the GP practice team. This meant they could follow up non-responders and pre-consented participants on behalf of the GP, further reducing the research burden on GPs, even more important during the pandemic and recovery phase and as such they were considered a success.

In addition, coworking with The Leeds Community Healthcare NHS Trust and NIHR Agile Research Teams relieved some of the burden on GPs and facilitated recruitment. It is encouraging to see more NIHR support for Agile Research Teams as our observation is that this valuable resource is much needed in primary care research.

Eligibility criteria were changed (SA06, 2021) to include an antibiotic prescription within the 24 months prior to consent, rather than 12 months used in the pilot trial. This was considered a success as it increased the pool of eligible patients and helped identify more potential participants. Eligibility was also increased by modifying exclusion criteria to allow recruitment of patients who were taking beta-blockers. This probably had a small impact on recruitment.

For participants recruited in the later stages of the trial, we moved towards using a single dose oral challenge which further streamlined efficiency of PAAP delivery. This allowed some low-risk populations to have a single dose rather than a graded challenge, which, importantly, demonstrated that it can be managed without compromising patient safety.

Inclusivity

See *Issues related to equality, diversity and inclusion throughout the project*.

Research capacity building

A clinical research fellow was appointed in 2021 who played a vital role and was key to successful delivery of the trial. The post-holder was subsequently successfully awarded an NIHR Doctoral Fellowship and is undertaking a PhD linked to ALABAMA.

A consultant antimicrobial pharmacist at Royal Cornwall Hospitals NHS Trust was recruited in 2021, with two more pharmacists joined the research team at Mid Yorkshire Teaching NHS Trust and Bradford Teaching Hospitals NHS Foundation Trust in 2022. Pharmacists at Truro and Bradford led delivery of PAT at their site during the trial. The pharmacist from Mid Yorkshire supported testing at the Leeds site.

Coronavirus disease discovered in 2019

ALABAMA was paused as a result of the COVID-19 pandemic. The research team adapted remarkably to enable recruitment to continue once the trial had restarted. Revised systems and processes were put in place to ensure participant safety, enable social distancing while testing continued (see above). In total, over 800 participants recruited to a trial during the pandemic and recovery period was a success.

In 2023, the health economic component of the programme was expanded to include a value of information analysis, which was a positive and pragmatic approach to the delays caused by COVID-19.

Qualitative research

The value and quality of the qualitative research led by Dr Sarah Tonkin-Crine during the programme have produced a suite of publications exploring how to change behaviours around penicillin allergy assessment and subsequent antibiotic prescribing that will support NHS implementation and ensure that information concerning both the patient and clinician perspectives are available to those designing penicillin allergy assessments.

Our work, entitled 'Managing Penicillin Allergy in Primary Care: An Important but Neglected Aspect of Antibiotic Stewardship', won the Research category in the UK annual Antibiotic Guardian Awards held in London on 2 May 2023. This is an initiative by the UK Health Security Agency (UKHSA) to recognise individuals and organisations that have made outstanding contributions to promote the responsible use of antibiotics and reduce the spread of antibiotic-resistant infections. The award highlights the high standard of our research and importance of addressing incorrect penicillin allergy as part of Antimicrobial Stewardship and raises the profile of the ALABAMA programme.

What was not successful

Delays

During 2019, the programme timeline was delayed by 7–8 months due to three components that were outside our control:

1. Excess treatment costs (ETC) – NHS England special commissioning not fulfilling their agreement to provide ETC for the ALABAMA trial

The tariff cost for performing the PAAP during the trial was not covered by Leeds Teaching Hospital Trusts Aligned Incentive Contract or Payment by Result. Prior to grant submission, a letter of intent to cover the ETC/tariff was obtained from the Locality Director NHS England, which stated that the ECT would be covered by NHS England Special Commissioning Service. However, NHS England subsequently declined support for ALABAMA as it was not considered to fall within the commissioning responsibility of NHS England. After escalation nationally for resolution, confirmation that NHS England and CCG would share the ETC 20 : 80%, respectively, came in 2019 causing significant delays.

2. Introduction of the new Schedule of Events Cost Attribution (SoECAT) Template

Schedule of Events Cost Attribution Template was also introduced in October 2018. Our study was one of the first recommended to complete SoECAT and it was a challenge to retrospectively complete the process. The NIHR CRN Yorkshire and Humber worked very supportively to get the approvals in place needing to take a very pragmatic view as the process did not fit a non-conventional drug trial.

3. Operating compliant with the new General Data Protection Regulation (GDPR) landscape

General Data Protection Regulation 2016/679 necessitated greater clarity and approvals for our novel direct data trial capture using an 'ALABAMA unit' in SystmOne EHR system and processing of patient records. GDPR compliant data sharing and data management systems were pioneered but were time consuming to build.

Coronavirus disease discovered in 2019

The COVID-19 pandemic caused a further 6-month delay from Stage 1 to Stage 2. Unsurprisingly, recruitment post COVID-19 was slower than previously expected due to NHS recovery pressures spanning GPs and immunology service resumption. Planned PPIE activities were also impacted although some key PPIE-suggested modifications were welcomed. For example, our video to explain to participants how we were managing safe return to PAT in clinics.

Costed extension request

Our request for an extension and additional funding to complete the trial with the original primary outcome was declined. We were therefore unable to assess the effect of the intervention on patient-directed health outcomes.

Staff contracts

To facilitate GP practice participation, we arranged for clinical NHS-employed members of the ALABAMA team to check eligibility and consent on behalf of GPs. Setting up the required staff contractual arrangements proved challenging. The West Yorkshire Integrated Care Board Research Team were extremely helpful in guiding us through the appropriate governance, with a lack of uniformity across the system and different localities. The issues encountered were highlighted to the NIHR Primary Care Programme Board.

Issues related to equality, diversity and inclusion throughout the project

The ALABAMA team designed research with equality, diversity and inclusivity in mind. Our electronic processes for identifying potential participants sampled entire general practice populations using report functions in SystmOne EHR system. Any potential participants identified using this method were invited to take part in the research. However, letters were sent out in English as we did not have resources for translation so it is likely that people who could not read English were disadvantaged in terms of opportunity to be involved in this research.

We recruited a range of General Practices including those who were already involved in research and some that were not. Our trial participants came from a range of sociodemographic backgrounds as indicated by a spread of Index of Multiple Deprivation quintiles among participants. Almost a quarter of participants were from the most deprived two quintiles, while just over half came from the two least deprived quintiles. Again, this may reflect the fact that penicillin allergy records are more common among people from areas of least deprivation. Gender representation was unequal with 72.0% of participants being female, but this is unsurprising given that more females have a penicillin allergy record.

In Yorkshire and The Humber, the majority of the population (85.4%) identifies as White. The remaining 14.6% is made up of various ethnic minorities, with Asian people being the largest group at 8.9%. In Cornwall, our second geographical recruitment area, the population is predominantly White, with over 96% of residents identifying as such in the 2021 census. In ALABAMA, the vast majority (98.4%) of participants in the trial were White, indicating a possible failure to engage non-White ethnic groups into the trial. In 2021, 5.6% of Leeds residents identified their ethnic group as 'Black, Black British, Black Welsh, Caribbean or African' category and 9.7% identified their ethnic group within the 'Asian, Asian British or Asian Welsh' category. Given that ethnic diversity falls with increasing age, it is unknown if the trial population was representative of the ethnicity of the older age groups predominantly recruited to the trial. More work is needed to explore ethnic diversity within different age groups in recruiting centres and how to engage non-White ethnic groups in research. We did not collect data relating to race during qualitative elements of the project, so we cannot comment on inclusivity in this aspect of the research.

Limitations relating to the method or execution of the research

ALABAMA was an open-label trial by necessity because of behaviour change intervention and practicalities/ethics of a placebo group. Thus, contamination between trial groups is possible. The primary end point had to be changed because of slow recruitment caused by COVID-19. COVID-19 is now known to have had an effect on GP consultations and antibiotic prescribing which are likely to have reduced the power of the trial; GP consultations were part of the primary outcome (if people did not see their GP they were less likely to be prescribed penicillins or other antibiotics; consultations were also part of the health economics analysis). Although there was representation across sociodemographic groups, non-White ethnic groups were under-represented in the trial.

Conclusions from the whole programme

Key patient behaviours in relation to PAT were identified as patients attending for allergy assessment and taking a penicillin, if prescribed, after a negative allergy test.

Key clinician (GP) behaviours were identified as referring for testing, updating allergy records and prescribing penicillins (if needed) after a negative test result.

Taking into consideration patient and clinician views about penicillin allergy and testing, the identification of barriers and facilitators to PAT and prescribing penicillins after a negative test, and addressing these in a behavioural component to the intervention, were considered vital to the success of the programme.

Materials were developed to increase knowledge of PAT, support beliefs about the importance of testing, and to increase confidence in performing the behaviours safely by providing a supportive environment.

General practitioners were happy to update medical records after a negative test result, but a clear, protocolised, EHR-based process was needed to ensure allergy status was updated.

During the NP trial, multiple measures were developed, approved and implemented to maximise recruitment. In spite of this, recruitment was affected by the COVID-19 pandemic and the primary outcome needed to change to reflect a likely reduction in trial recruits.

The RCT found penicillin prescribing was significantly increased which markedly increased the opportunity for patients to receive first-line treatment.

The PAAP was safe.

Penicillin allergy assessment was an effective antimicrobial stewardship tool in primary care, allowing significant reductions in total antibiotic prescribing.

Within-trial assessment indicated the assessment pathway was likely to be cost-effective. The cost- effectiveness modelling suggested the net benefit of testing was high but uncertainties were high. The value of information studies indicated another trial including health outcomes would be worthwhile.

Process evaluation found GPs were motivated to join the trial because of perceived benefit to patients.

General practitioners were positive about the trial design/delivery and support from the trial team. Many participants sought clarity about penicillin allergy status. Participants reported feeling safe and well looked after during testing. Most participants accepted test results and were relieved to receive a negative test that enabled them to take penicillin.

Larger trials or longer-term follow-up of our participants will be needed to establish if penicillin allergy assessment improves patient health outcomes, like treatment response failure, hospitalisation and mortality.

The findings are clinically important as the intervention allowed more participants to receive first-line therapy and reduced overall antibiotic consumption, which could help to reduce the selection pressure for AMR if implemented more widely. The findings are being disseminated to patients and the general public and communicated to policy-makers and key stakeholders in a series of events aimed at widening access to penicillin allergy assessment and resolving unanswered questions through further research. We held a joint dissemination event with the NIHR-funded SPACE study (Spurious Penicillin Allergy in Secondary Care). Over 90 stakeholders from across the health system and beyond were in attendance. The event comprised a morning of dissemination activities from both studies. The afternoon was dedicated to discussing ideas for widening access to penicillin allergy assessment and relevant policy considerations needed to support this. We are now working with stakeholders to develop an implementation plan for

widening access in the NHS. We are also working with creative partners to develop an animation and an arts-based project aimed at educating secondary school children on the importance of antibiotics and de-labelling incorrect PALs.

Currently, we conclude that patients with a PAL who are frequent users of antibiotics and at lower risk of a true penicillin allergy would likely benefit from penicillin assessment. Such patients should seek guidance form their GP for an appropriate referral to the immunology service for formal penicillin allergy assessment. However, capacity for penicillin allergy assessment in the NHS is currently limited. The implementation plan that resulted from the dissemination event (above) requires action from stakeholders across the NHS (including NHS England, UK Health Security Agency, NICE, Integrated Care Boards) to address issues such as developing workforce capacity and standardised training resources and testing guidance/protocols.

Recommendations for future research

A greater understanding of the ethnicity across different age groups and its relationship with PALs is needed.

Data from long-term follow-up of trial participants would help to give more certainty to the health economic findings and valuable additional information on patient health outcomes.

The work undertaken with The TPP to facilitate trial delivery using the SystmOne EHR has the potential to make pragmatic primary care trials in general much more efficient and warrants further development and assessment.

The value of information work package indicates that a follow-on trial is needed to adequately assess cost-effectiveness and patient health outcomes. A follow-on trial is also needed to ensure findings are applicable in non-White ethnic groups and to establish which people will benefit most from the intervention to allow more targeted interventions.

There are many aspects of penicillin allergy assessment that are not standardised and where unnecessary variation will introduce inequalities and inefficiencies into practice. These need to be resolved to establish a pragmatic standard of care against which new developments can be assessed.

Implications for practice and any lessons learnt

This section outlines the basis of our implementation strategy to maximise knowledge mobilisation from the ALABAMA programme towards improving NHS practice.

A large body of observational evidence points to harms associated with incorrect PALs, but ALABAMA has now provided robust evidence that antibiotic prescribing can be improved by removing incorrect labels. The trial was underpowered to determine if addressing incorrect PALs reverses the poor health outcomes associated with these labels but the findings of the ALABAMA trial and programme overall indicate that a PAAP applied in advance of need safely improves antibiotic prescribing and is cost-effective.

Currently we conclude that patients with PALs who are frequent users of antibiotics and at lower risk of true penicillin allergy would likely benefit from penicillin assessment.

Given the lack of large-scale interventions that can improve antibiotic prescribing, measures should be undertaken to widen access to penicillin allergy assessment in the NHS beyond the current guidelines. This will require undertaking the necessary implementation to research to understand how best to achieve this within the capacity of the immunology service to avoid 'swamping the service' and consideration of how best to extend capability by, for example, utilisation of other healthcare professionals under the supervision of immunology specialists. We are now working with key stakeholders (such as NHS England, UK Health Security Agency, NICE, Integrated Care Boards) and NIHR infrastructures to facilitate this immediate NHS implementation.

Additional information

CRediT contribution statement

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Shadia Ahmed: Investigation (equal), Writing – reviewing and editing (equal).

Kelsey Armitage: Project administration (lead), Supervision (equal), Writing – original draft (supporting), Writing – reviewing and editing (supporting).

Chris Bates: Resources (equal), Software (equal), Writing – reviewing and editing (supporting).

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Mandy East: PPIE (supporting).

Maureen Jenkins: PPIE (supporting).

Lynne Regent: PPIE (supporting).

Amena Warner: PPIE (supporting).

Rose Wollard: PPIE (supporting).

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Management arrangements

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The University of Leeds sponsored and led the research programme, the co-chief investigators were Dr Jonathan Sandoe and Professor Sue Pavitt.

The research was co-ordinated by the Primary Care Clinical Trials Unit (PC-CTU) in the Nuffield Department of Primary Care Health Sciences at The University of Oxford, led by co-investigators Professor Chris Butler and Professor Ly-Mee Yu.

Work packages 1.1–1.3, 1.6 and 2.3 were led by Dr Sarah Tonkin-Crine, Associate Professor and Health Psychologist, PC-CTU, University of Oxford.

Work packages 1.4, 1.5 and 2.1 were led by Dr Jonathan Sandoe and Professor Sue Pavitt and were co-ordinated by the PC-CTU at The University of Oxford, with support from co-Investigators and the research team at the University of Leeds.

Work package 2.2 was led by Dr Rubén Mújica-Mota, Associate Professor, Academic Unit of Health Sciences, University of Leeds, who took over from Bethany Shinkins (2018–23) and previously Claire Hulme (to 2018).

A Trial (Programme) Steering Committee, led by an independent chair, Professor Michael Moore, University of Southampton, provided oversight on work packages 1.5 and 1.6.

The DMEC was independent chaired by Professor Beth Stuart at Queen Mary University of London (formerly of the University of Southampton).

Mrs Mina Davoudianfar, PC-CTU, University of Oxford, acted as Clinical Trial Manager from 2018 to 2021 and Ms Kelsey Armitage from 2021 to 2024.

Ms Catherine Porter, University of Leeds, acted as Programme Manager from 2018 to 2024 and Anita Blakeston held the role from 2017 to 2018.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

The trial protocol is published in *BMJ Open*. The trial statistical analysis plan is available on ClinicalTrials.gov. The health economics analysis plan is available at ISRCTN https://doi.org/10.1186/ISRCTN20579216 on request. Trial data will be available to collaborators following discussion with chief investigators.

Ethics statement

The ALABAMA trial was conducted in compliance with the principles of the World Medical Association Declaration of Helsinki and Good Clinical Practice. NHS REC approval was granted by the National Research Ethics Service London Bridge Committee (ref: 19/LO/0176) on 29 January 2019.

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/BEYF6487.

Primary conflicts of interest: Jonathan AT Sandoe is a member of the British Society for Allergy and Clinical Immunology Penicillin Allergy working party. He is panel member of the European Society for Clinical Microbiology and Infectious Diseases guideline for antibiotic allergy. He was colead for the British Society for Antimicrobial Chemotherapy massive open access online penicillin allergy course. He has research funding from the Engineering and Physical Sciences Council, NIHR (i4i, HTA), Wellcome Trust and Medical Research Council. Christopher C Butler has received an NIHR Senior Investigator award. Rubén Mújica-Mota has received funding from the Leeds NIHR Biomedical Research Centre and research funding from the NIHR for the SPACE study (Spurious Penicillin Allergy in Secondary Care) (NIHR129069). Sinisa Savic is current chair of British Society for Immunology-Clinical Immunology Professional Network. He has received research funding from Kennedy Trust, Medical Research Council, EU2020 Horizon programme, Novartis, Takeda, CSL Behring and SOBI. Sarah Tonkin-Crine has received funding from the NIHR Health Protection Research Units in HCAIs and Antimicrobial Resistance, a partnership between the UK Health Security Agency (UKHSA) and the University of Oxford (NIHR200915). She is a committee member of the NIHR HSDR funding board. Ly-Mee Yu has received funding from the NIHR. Susan H Pavitt has received funding from Reckitt, Health Education England, West Yorkshire Integrated Care Board, Leeds Hospitals Charity, NIHR, UK MS Society. She was a member of the Medical Research Council/NIHR Efficacy and Mechanism Evaluation Board from 2012 to 2018.

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Publications

Journal articles

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Appendix 1 Research methods

Appendix 1a Workstream 1 research methods

A 1.1

WP1.1 methods, see *Antibiotics*[6] https://doi.org/10.3390/antibiotics7030071

A 1.2

WP1.2 methods see *Journal of Allergy and Clinical Immunology: In Practice*[7] https://doi.org/10.1016/j.jaip.2019.02.036 open access version available at https://eprints.whiterose.ac.uk/143372/

A1.3

WP1.3 methods see *BMJ Open*[9] https://doi. org/10.1136/bmjopen-2019-035793

A1.4

WP1.4 methods see *BMC Trials*[10] https://doi.org/10.1186/s13063-024-08506-x

A1.5

WP1.5 Methods (unpublished elsewhere).

Some aspects of the pilot trial method are described in detail in *BMC Trials*.[10] https://doi.org/10.1186/s13063-024-08506-x

1.5.1 Design

A NP RCT with feasibility outcomes. The plan was to recruit 8 GP sites over 3 months, each site recruiting 12 participants, 96 in total. GPs confirmed suitability of patients identified from a report generated in the SystmOne EHR system. Eligible and willing patients were then consented and randomised to either PAAP or UCC.

1.5.2 Study population

Inclusion criteria

Adults (> 18 years) willing and able to give informed consent; and penicillin allergy record of any kind in EHR; and receipt of either: penicillin, cephalosporin, tetracycline, quinolone or macrolide class antimicrobial or fosfomycin, nitrofurantoin, trimethoprim, clindamycin in the previous 12 months.

Exclusion criteria

- Likely life expectancy estimated < 1 year by GP.
- Unable to attend Immunology clinic.
- Unsuitable for entry into testing pathway because:
  Allergy history consistent with anaphylaxis to penicillin.
  History of toxic epidermal necrolysis/Stevens-Johnson syndrome precipitated by a penicillin, drug reaction with eosinophilia and systemic symptoms or any severe rash which blistered or needed hospital treatment, and acute generalised exanthematous pustulosis precipitated by a penicillin.

Previous specialist investigation for penicillin allergy.
History of brittle asthma or unstable coronary artery disease, or dermographism or other severe/poorly controlled skin conditions.
Considered unsuitable for trial participation by the GP for example because of chaotic lifestyle.

- Pregnant/planning to become pregnant.
- Breastfeeding mothers.
- Taking beta-blocker medication.
- Currently receiving or due to start immunosuppressive medication.
- Currently taking (or recently taken) systemic steroids and unable to stop these for 10 days pre-testing.
- Currently taking antihistamines and unable to stop these for 4 days pre-testing.

1.5.3 Randomisation

Participants were randomised with an allocation ratio of 1 : 1 to PAAP intervention or UCC a fully validated online randomisation system (Sortition version v2.3 15-10-2014). Allocation was minimised by GP practice, age, number of antimicrobial prescriptions/year and number of NHS Quality and Outcomes Framework registered diseases, to ensure balance of allocation in these baseline covariates and minimise predictability of allocation of the intervention.

1.5.4 Follow-up

The pre-COVID-19 plan was to follow up participants for 4 months after randomisation as part of the NP trial. Participants who had undergone PAAP were contacted by a researcher at days 2–4 and 28–30 post-testing and monthly thereafter to collect safety data, primary outcome data, EQ-5D-5L and arrange clinical review, if necessary.

1.5.5 Statistical analysis

A descriptive analysis was planned for the NP trial, focusing on determining the overall feasibility parameters to inform the main trial.

1.5.6 Progression criteria

A meeting was held with the TSC and DMEC to establish predefined progression criteria to the main trial.

Appendix 1b Workstream 2 research methods

A2.1

WP2.1 methods, see protocol paper[12] and amendment[13] and ISRCTN registry: https://doi.org/10.1186/ISRCTN20579216

A2.2

WP2.2 methods: see ISRCTN registry: https://doi.org/10.1186/ISRCTN20579216 Health economics analysis plan.

A2.3

WP2.3 methods see *BJGP Open*[17] https://doi.org/10.3399/BJGPO.2024.0119 (Healthcare professionals) and https://doi.org/10.3399/BJGPO.2024.0136 (patients).

Appendix 2 PRISMA diagram (work package 1.1)

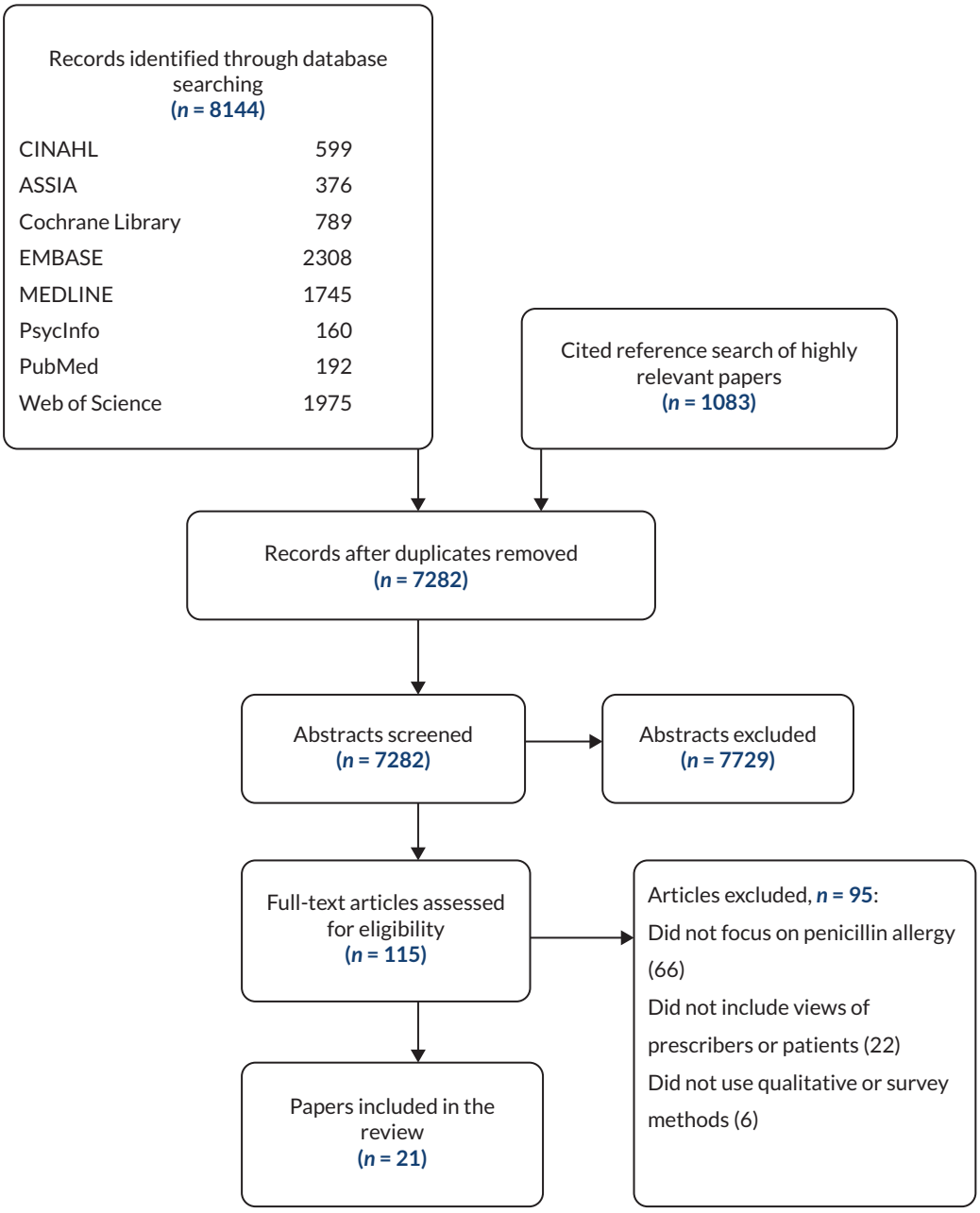

FIGURE 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram showing the identification of papers from database searches.

Appendix 3 ALABAMA trial CONSORT diagram (work packages 1.5 and 2.1)

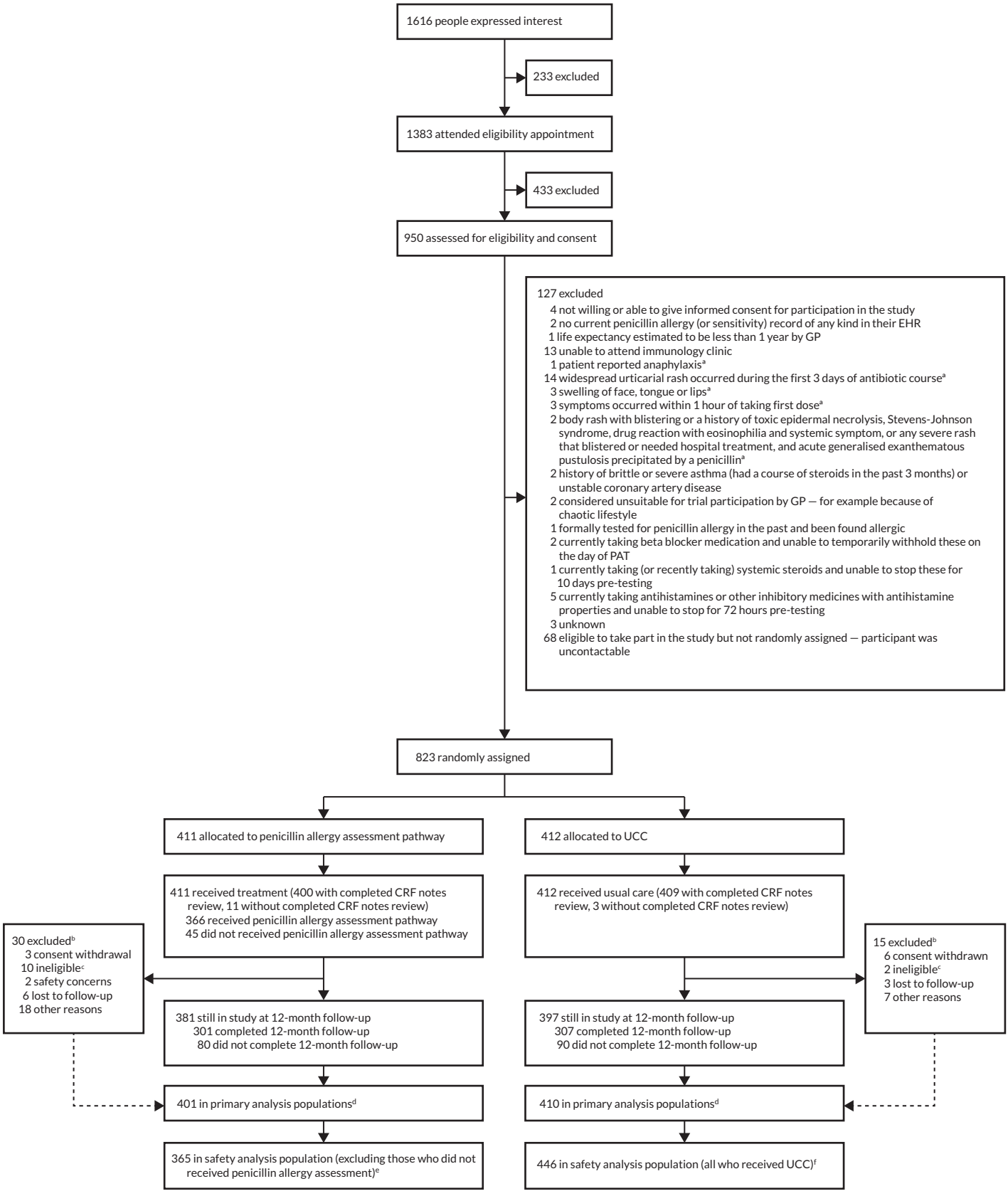

FIGURE 6 Consolidated Standards of Reporting Trials diagram – recruitment to NP and main trial. CRF refers to the form that captured the review of the participants' primary and secondary care medical notes. Safety analysis includes the as-treated population. CRF, case report form. a, In relation to previous penicillin courses. b, Not mutually exclusive. c, Participants found to be ineligible after random assignment and excluded from the primary analysis population. d, Excluding the ineligible patients. e, Excluding those who did not receive penicillin allergy assessment and 1 of the 10 ineligible patients. f, Four hundred and twelve allocated to UCC plus 45 who were allocated to the PAAP who did not receive it, minus the 11 ineligible patients, 9 of whom came from the PAAP group. Reproduced with permission from Sandoe *et al.*[14] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original text.

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