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Extended Research Article

Direct oral penicillin challenge in secondary care with low-risk patients: the SPACE mixed-methods study with cost-effectiveness analysis

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This article

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Abstract

Some text in this abstract has been adapted from Krishna MT, Bhogal R, Ng BY, Kildonaviciute K, Jani YH, Williams I, *et al*. A multicentre observational study to investigate feasibility of a direct oral penicillin challenge in de-labelling 'low risk' patients with penicillin allergy by non-allergy healthcare professionals (SPACE study): Implications for healthcare systems. *J Infect* 2024;**88**:106116. https://doi.org/10.1016/j.jinf.2024.01.015. This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The text below includes minor additions and formatting changes to the original text.

Background: One in five inpatients carries a penicillin allergy label. However, 90–95% of labels are incorrect. Penicillin allergy labels lead to increased risk for serious hospital infections and longer hospital stay and are associated with higher estimated healthcare costs. Penicillin allergy testing is onerous and requires a specialist. Routine inpatient testing is not available. Recent evidence suggests that a direct oral penicillin challenge delivered by non-allergy specialists is safe in 'low risk' patients, who are highly unlikely to be allergic based on history.

Aims

1. To explore behaviour, attitudes and acceptability of patients, healthcare professionals and managers regarding a direct oral penicillin challenge in 'low risk' patients.
2. To inform development of an implementation framework and determine potential cost-effectiveness.

Methods: This study (1 May 2021–30 April 2023) involved delivery of direct oral penicillin challenge by non-allergy specialists across three clinical settings (medical/infectious diseases wards, presurgical and haematology-oncology units) at three hospitals. The study had three workstreams:

1. Workstream 1: Screening for potential suitability. Patients were stratified into 'low risk' and 'high risk'. 'Low-risk' patients underwent direct oral penicillin challenge.
2. Workstream 2: One-to-one semistructured interviews with patients (N = 43) and focus group (N = 28) discussions with stakeholders.
3. Workstream 3: Care pathway mapping, decision-analytic modelling and value of information analysis were carried out to determine potential cost-effectiveness of direct oral penicillin challenge.

Results: One thousand and fifty-four of 2257 screened patients were eligible, 270 of 643 approached patients consented (42%). Two hundred and fifty-nine patients were risk-stratified (155 'low risk'; 104 'high risk'). Of the 155 'low risk' patients, 126 underwent direct oral penicillin challenge, 122 (97%) were de-labelled with no serious allergic reactions and 43 patients were interviewed.

Low-risk patients accepted their allergy labels, had limited knowledge of the adverse impact and most were keen to have their labels reviewed. Healthcare professionals demonstrated a risk-averse approach, although would engage in the intervention with training, resource availability and a governance framework in place.

The total costs of the direct oral penicillin challenge pathway were higher than the costs of direct oral penicillin challenge alone (£940 vs. £98–288 per patient). There were minimal expected savings in antibiotic and hospital costs in the short term and potentially large healthcare cost savings over 5 years.

Limitations: Relatively small sample size for direct oral penicillin challenge, poor conversion rate, particularly in acute settings, patients with limited English language proficiency could not be included and the study was not sufficiently powered and controlled to conduct a cost-effectiveness evaluation.

Conclusions: This first multicentre United Kingdom study showed that non-allergy specialist-led direct oral penicillin challenge is feasible in secondary care. A high proportion of direct oral penicillin challenges were successful, with positive feedback from patients. Majority of screened patients did not progress through the study pathway. Going forward, a multipronged approach is needed to enhance equitability of direct oral penicillin challenge in routine practice.

Follow-up mechanisms to consider the intervention during a clinically stable state and a governance framework for those lacking capacity to consent are needed. The cost of delivering a direct oral penicillin challenge pathway in its entirety is significantly higher than the costs of performing direct oral penicillin challenge per se.

Future work: A randomised controlled trial with long-term follow-up is needed to determine the cost-effectiveness of direct oral penicillin challenge.

Study registration: This study is registered as ISRCTN55524365.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/MTYW6557).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
ALABAMA	Allergy Antibiotics and Microbial Resistance
AMR	antimicrobial resistance
AMS	antimicrobial stewardship
AMU	acute medical unit
BSACI	British Society for Allergy and Clinical Immunology
COPD	chronic obstructive pulmonary disease
COVID	coronavirus disease
DALES	Drug Allergy Labels in Elective Surgical
DPC	direct oral penicillin challenge
eMIT	electronic market information tool
EP	electronic prescribing
EVPI	expected value of perfect information
GP	general practice
GRIPP2	Guidance for Reporting Involvement of Patients and the Public 2
HCP	healthcare professional
HRG	Healthcare Resource Group
HSR	hypersensitivity reaction
ID	infectious diseases
IgE	immunoglobulin E
IT	information technology
LOS	length of hospital stay
MRSA	meticillin-resistant *Staphylococcus aureus*
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NS	neutropenic sepsis
ONS	Office for National Statistics
PAL	penicillin allergy label
PI	principal investigator
PPIE	patient and public involvement and engagement
PPIR	Patient and Public Involvement in Research
REDCap	Research Electronic Data Capture
RN	research nurse
RP	research pharmacist
SAE	serious adverse event
TENS	toxic epidermal necrolysis
UHB	University Hospitals Birmingham NHS Foundation Trust
WHO	World Health Organization

Plain language summary

Many patients who experience minor side effects when taking penicillin are wrongly labelled as 'allergic', leading to huge numbers of people with incorrect penicillin allergy labels in hospitals. Patients with an allergy label receive different antibiotics which might be toxic and less effective. Allergy tests are not routinely available due to very few specialists in the National Health Service.

We developed a simple way to remove incorrect labels in patients at low risk of genuine allergy. This involves taking a careful history from the patient to decide if they are at low risk of having a genuine allergy to penicillin. Then, if suitable, they are offered a test dose or a challenge test (penicillin capsule to be swallowed without doing other allergy tests) in a hospital after taking prior informed consent. In this study, the test was performed by trained healthcare professionals with no specialist background in allergy. We included patients admitted in hospital wards and outpatients from surgery and cancer units in three hospitals.

We did 126 challenge tests and showed that almost all (97%) did not have an allergy. One patient developed stomach upset and three had mild rash. Very few patients in the wards were eligible to participate for medical reasons, and a greater percentage of outpatients were suitable.

We spoke to patients and healthcare professionals about this pathway. Professionals understood its importance but thought appropriate training, safety and resources were required. Patients were keen to find out if they were really allergic and felt safe undergoing the challenge test in hospital. The main reasons for not taking part were personal circumstances.

We showed that the penicillin challenge test can be delivered by non-allergy healthcare professionals, but a smaller percentage of patients were eligible to undergo this test than that shown in previous studies. We developed recommendations for wider roll-out of this pathway and gained good understanding of how it would work in the 'real world'. The cost saving appears small in the short term and more research is needed to understand the long-term benefits.

Scientific summary

Background

Penicillin allergy labels (PALs) occur in 6% of the population in England, and 15–20% of inpatients have a PAL in their records. Previous studies have shown that 90–95% of PALs are inaccurate. The current standard of care involves allergy specialist review, skin tests and a challenge procedure. There is an unmet need for allergy services and penicillin allergy testing is not routinely available.

Penicillin allergy labels lead to use of alternative antibiotics which might be less effective, might enhance risk of antimicrobial resistance (AMR) and hospital-acquired infections, contribute to longer hospital stay, higher re-admission rates and mortality.

Mis-labelling patients has been linked to suboptimal skills and knowledge gaps in allergy history taking and poor documentation in clinical records.

Patients can be stratified into 'low risk' and 'high risk' based on a structured clinical history and scrutiny of clinical and prescription records. 'Low risk' patients are highly unlikely to have an immune-mediated reaction to penicillin. A direct oral penicillin challenge (DPC; without undertaking skin tests) has been shown to be safe and feasible and successfully delivered by non-allergy healthcare professionals (HCPs), such as clinical pharmacists and physicians. There is limited evidence from the UK, but there is a larger body of evidence from the USA and Australia regarding the success of DPC in mitigating the adverse impact of PALs. Safe implementation depends on an appropriate clinical setting and uptake amongst patients and relevant stakeholders.

Objectives

Primary

- To explore behaviour, attitudes and acceptability of patients, HCPs and managers regarding use of DPC in 'low risk' patients.
- To develop treatment pathways and a clinical governance framework for this service model.

Secondary

- To assess the proportion of 'low risk' patients with a PAL who would be eligible for a DPC.
- To assess the proportion of 'low risk' patients who would be willing and will complete a DPC.
- To explore practical aspects of implementing this de-labelling programme in secondary care by investigating factors, such as organisational context, treatment pathway, protocol implementation, time taken and resources.
- To evaluate the potential cost-effectiveness of this service model.

Methods

This study spanned 24 months and involved three clinical settings [acute medical units (AMUs)/infectious diseases (ID) units, presurgical units and haematology-oncology units] in three hospitals including University Hospitals Birmingham NHS Foundation Trust, Leeds Teaching Hospitals and Oxford University Hospitals NHS Foundation Trust. The study included three workstreams (WS):

Workstream 1

Patients with a PAL were identified and screened from respective Trust clinical records using a structured proforma employing predetermined study criteria. Clinically unstable patients, pregnant or breastfeeding patients, those with current COVID-19 infection, patients lacking capacity to give informed consent or taking part in another research intervention study were not approached. Those potentially suitable were approached for expression of interest. Informed consent was obtained from interested participants and a risk stratification process was conducted based on pre-determined study criteria. Participants were classified as 'low risk' and 'high risk'. Risk stratification was conducted by non-allergy specialist HCPs (Research Pharmacists at Birmingham and Oxford and Research Nurses at Leeds) and a non-allergy specialist study consultant provided clinical supervision for the entire process. 'Low risk' patients were those who were highly unlikely to have a true allergy and 'high risk' patients gave a history suggestive of an immune-mediated reaction and/or had concomitant comorbidity, such as severe asthma or cardiac disorder. 'Low risk' patients were offered a DPC. This involved administration of a single dose of 500 mg amoxicillin and 1-hour observation to monitor for an immediate hypersensitivity reaction (HSR) followed by 250 mg twice daily for 3 days to assess for a delayed HSR. All patients were reviewed on day 5 to check for their clinical tolerance. One hundred and twenty-six DPCs were conducted [119 'opportunistic' and 7 'therapeutic' (to treat current bacterial infection)].

Data analysis

Descriptive data were generated for all clinical settings across the three sites. To aid in the detection of potential associations, continuous variables were compared between the hospital/clinical setting groups using Kruskal–Wallis tests. Similarly, categorical variables were compared across hospital/clinical settings groups using Pearson chi-squared tests. Detailed analysis was provided to compare outcomes, such as de-labelled 'Yes/No', with the use of logistic regression. First, the outcome was regressed upon each potential 'risk factor', such as gender, producing an unadjusted odds ratio (OR; by exponentiation of the fitted parameter), and then a multivariable logistic regression used to yield adjusted ORs.

Workstream 2

Patients

'Low risk' patients were invited to participate in the qualitative arm of the study at the time of recruitment to WS1. Purposive sampling was undertaken to achieve a diverse sample. One-to-one semistructured interviews were conducted with patients {total N = 43 [mean age 61 (± 14 standard deviation) years]} by telephone using a pre-specified interview schedule. The interview questions were informed by risk perception theories and developed iteratively with our patient and public partners to ensure face validity.

Healthcare professionals and other stakeholders

Three focus group discussions were conducted with 28 participants in total across the 3 centres. We purposively sampled staff to include representation from relevant stakeholders [including general practitioners (GPs), junior doctors, consultants, nurses, pharmacists, managers, commissioners] at each site. Focus groups were held in person (two sites) and online (one site). The discussions were audio-recorded and written notes were taken. Two members of the research team facilitated the discussions using a pre-specified topic guide to prompt healthy discussion, informed by relevant domains of the 'Theoretical Domains Framework'.

Audio recordings of interviews and focus groups were transcribed verbatim and coded. Thematic analysis was undertaken using both inductive and deductive approaches and was informed by 'Theoretical Domains Framework'.

Workstream 3

An economic evaluation of DPC relative to current standard of care, that is no PAL testing, was carried out in 'low risk' study participants. We estimated the costs of the DPC pathway at each study site and its expected impact on the costs of antibiotic regimens in the period immediately after DPC, for AMU/IDU and presurgical patients, or up to one course of chemotherapy after DPC in haematology-oncology patients. We combined prospectively collected individual patient data on the time that clinical and non-clinical staff spent in screening and risk stratification and retrospectively, collected data on staff time inputs into all DPC steps, to value time inputs according to the midpoint of the salary scales for the title and grade of staff and derived the costs of the full DPC pathway. We used Monte Carlo simulation methods to produce estimates of sampling uncertainty of costs in the form of 95% credible intervals (95% CrI).

We also estimated the value of conducting further research to capture the economic impact of DPC in terms of hospital re-admissions, length of hospital stays of initial and subsequent admissions, and GP visits over a 4.5-year follow-up period, the maximum over which evidence was found in the literature. This was a value of information analysis with the expected value of perfect information (EVPI) as outcome, conducted separately for each new service pathway implemented across the three study sites.

In sensitivity analysis, we explored the impact of increasing the proportion of eligible patients who are approached for consent to undergo testing, accounting for the costs of training and varying the staff skill mix to allow for the possibility that less experienced staff may deliver the new testing pathway. In addition, we held discussions with local managers at each study site to identify key questions emerging from our findings and areas of uncertainty that would need to be addressed by further studies.

Patient and public involvement and engagement

The investigators worked in collaboration with representatives from Allergy UK and the UK Sepsis Trust and two groups of members of the public in Oxford and Birmingham. Their input was sought for the study protocol, study amendments, participant recruitment strategies, patient facing documents, data interpretation and recommendations for further research.

Results

Workstream 1

A total of 2257 patients (834 males and 1423 female) were screened across the 3 clinical settings and the 3 participating sites. One thousand two hundred and three (53.3%) were deemed ineligible based on study criteria at screening. A total of 1054 (46.6%) patients were considered eligible, 643 were approached and 412 not approached due to practical factors. Of 643 patients who were approached, 373 declined to participate and 270 (116 males and 154 female) consented. The overall conversion rate from screening to informed consent stage across all clinical settings was 12%. It was very low (3.3%) in the acute settings but greater in the elective settings at 17.7%. Progression in study pathway significantly was greater in Oxford (OR −2.06; $p = 0.001$), less in Leeds (OR −0.37; $p < 0.001$) and greater in elective settings including haematology-oncology (OR −2.20; $p < 0.002$) and presurgical (OR −3.55; $p < 0.001$). Male patients (OR −1.36; $p = 0.02$), those at Oxford (OR −1.73; $p = 0.002$), haematology-oncology (OR −3.30; $p < 0.001$) and presurgical (OR −5.51; $p < 0.001$) were significantly more likely and those ≥ 80 years (OR −0.23; $p = 0.001$) significantly less likely to consent.

There were 102, 77 and 91 consented patients from Birmingham [age median 60.00 interquartile range (51.50–69.75) years], Oxford [58.00 (46.00–68.25) years] and Leeds [61.00 (48.00–73.00) years], respectively. Of 270 consented patients, 259 (81.2%) were subsequently risk stratified, with 155 (60%) stratified as 'low risk' and 104 (40%) as 'high risk'. Of 155 'low risk' patients, 126 underwent DPC and 122 (97%) of these patients were successfully de-labelled. There were no serious immediate or delayed HSRs among any patient who underwent DPC.

Workstream 2

Most of the 'low risk' patients we interviewed accepted the validity of their PAL. They were receptive to having this reviewed, for multiple reasons including potential individual benefits as well as the contribution to wider society.

Prior to involvement in the study, they reported having little or no understanding of the adverse impact of PAL on their health, although some noted that they had to receive multiple antibiotic courses as a consequence. Some HCPs perceived potential risks to individuals undergoing DPC as well as to their own professional practice and accountability and were typically more risk averse than patients. A key theme for HCPs was around the level of training required to undertake risk stratification and DPC. The range of background knowledge around allergy testing varied substantially between sites. In general, pharmacists were more familiar with taking an allergy history and prescribing medication, based on interaction with allergy services in their Trusts. The research nurses came from a different clinical background and had very little prior knowledge around allergy. This differential training may have been reflected in the greater confidence of pharmacists to risk stratify and de-label patients. Infrastructure, clinical skill, dedicated space and equipment, a clear governance framework and appropriate timing of the intervention within a care pathway, were considered essential for routine use of DPC.

Workstream 3

Total costs of the full DPC pathway averaged across the three study sites, from screening to de-labelling, were £940 per de-labelled patient. In contrast, the costs of performing DPC alone, ignoring the costs required to identify and consent patients to undergo testing for their PAL, varied between £98 and £288 per patient undergoing DPC across study sites. The costs of delivering DPC amounted to 50 times the size of the potential cost savings from switching to penicillin from second-line antibiotic medications and reduced length of hospital stay during the index admission. Subgroup analysis revealed that the full cost of DPC per de-labelled patient varied between £502 (95% CrI: 269 to 1438) in haematology-oncology at Leeds to £1829 (1115 to 4943) in AMU/IDU in Birmingham and £2329 (947 to 19,504) in AMU/IDU in Leeds. The costs of DPC were sensitive to the rate of eligible patients who were approached at Leeds but not at Oxford or Birmingham. The EVPI was highest in Oxford, where the value of further research per de-labelled patient varied in the range of £20–25 across clinical settings, whereas in Leeds it varied between £100 per de-labelled patient in haematology-oncology, £6 in the presurgical group and £0 in AMU/IDU while in Birmingham it was £0 in all three patient groups. Discussion with local managers in Leeds revealed that increasing the proportion of presurgical patients who receive DPC in time to benefit from optimal prophylactic management with penicillin may require investing in an additional HCP role to help identify eligible patients at their initial outpatient assessment appointment. At Birmingham, further research on the role that DPC may play in relieving the pressure on specialist allergy testing services was highlighted. At Oxford, identifying service configurations in which the service may pay for itself from a provider perspective was perceived as key to the economic case for adoption.

Conclusions

This is the first multicentre UK study to demonstrate safety and feasibility of delivering DPCs in ‘low risk’ patients by non-allergy specialist HCPs in a safe clinical environment in secondary care.

Implications for service

1. There was a very high uptake of DPC amongst those ‘low risk’ patients who consented to take part, and the majority of these were successfully de-labelled. There were no serious type-I or type-IV HSRs.
2. A very large proportion of patients screened were deemed ineligible due to clinical instability, comorbidity, or being uncontactable.
3. ‘Opportunistic de-labelling’ in outpatient settings may offer greater opportunities than inpatient de-labelling.
4. Patients with a PAL were keen to have their record reviewed and be considered for de-labelling employing DPC. ‘Low risk’ patients declined DPC mainly due to personal circumstances.
5. There is a need to raise awareness of the adverse impact of PAL amongst patients.
6. While HCPs recognised complexities of the DPC, data also support the feasibility of delivery by non-allergy specialists with appropriate resources, training, facilities, local policies and governance framework and escalation or referral pathways to allergy specialists.

7. The full costs of delivering DPC are significantly higher than the costs of performing the oral challenge test itself alone, which requires careful consideration by providers as to which delivery model is most efficient given their local case mix, service configuration and information technology service infrastructure.
8. The study highlights the importance of a flexible or staged approach to adoption of the DPC intervention, so that it is properly embedded into organisational cultures and systems.

Future research

1. Value of information analysis suggests that a randomised controlled trial with long-term follow-up for up to 5 years is needed to determine the cost-effectiveness of DPC by capturing relevant data relating to GP consultations for infections, hospital admission rates and duration, AMR, hospital-acquired infections and mortality.
2. Future studies with opportunistic de-labelling may offer better value for money by designing the intervention as a non-allergy specialist pharmacist-led DPC along the lines of the model implemented at the Oxford study site.

Study registration

This study is registered as ISRCTN55524365.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health and Social Care Delivery Research programme (NIHR award ref: NIHR129069) and is published in full in *Health and Social Care Delivery Research*; Vol. 13, No. 9. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

The Burden and Adverse Impact of Inaccurate Penicillin Allergy Labels on the Health Service

BOX 1 Key messages

- There is a huge burden of penicillin allergy labels in high-income countries including the United Kingdom National Health Service.
- Ninety to 95% of penicillin allergy labels are inaccurate.
- The are no point-of-care tests for penicillin allergy and there is an unmet demand for allergy specialists.
- Patients with penicillin allergy labels receive alternative antibiotics which enhance risk of antimicrobial resistance, hospital-associated infections and length of hospital stay.
- A direct oral penicillin challenge has been shown to be safe in patients deemed as 'low risk' for true penicillin allergy and there is emerging evidence that this intervention could be delivered by a non-allergy healthcare professional with appropriate training and in a safe clinical environment.
- Further research is needed to find a place and acceptability of this intervention in the routine clinical care pathway in the United Kingdom National Health Service.

Background

The burden and adverse impact of penicillin allergy

Up to 6% and 10% of the general population in England and the USA respectively carry a penicillin allergy label (PAL), and 15–20% of inpatients have a PAL on their records.[1–4] A number of studies have reported that 90–95% of PALs are inaccurate.[5–9] Common side effects experienced by patients, such as nausea, abdominal discomfort or diarrhoea, are incorrectly labelled as an allergy.[10] Other reasons include bacterial or viral infection-related rash in childhood, or virus–penicillin interaction causing a rash (e.g. amoxicillin in glandular fever), are also often incorrectly attributed to the penicillin taken at the time of the infection.[10] Gaps in knowledge and skills of healthcare professionals (HCPs) with respect to allergy history taking is likely to be a contributory factor to the generation of inaccurate PALs, and education and training has been shown to have a positive impact.[11,12] True allergic or hypersensitivity reactions (HSRs) occur but are relatively rare and usually mild. Delayed benign T-cell-mediated skin rashes can occur due to penicillin but often are non-reproducible when the patient is rechallenged, probably due to an absence of immunological memory.[10] Less common are genuine immunoglobulin E (IgE)-mediated reactions or type-I HSRs. Even in patients with a genuine allergy, penicillin-specific IgE antibodies may wane over time, such that 80% of previous IgE-mediated allergy is likely to have resolved when patients are re-exposed to penicillins after 10 years have elapsed since the index episode.[10]

Penicillin allergy labels compromise antimicrobial stewardship (AMS) and enhance the risk of antimicrobial resistance (AMR) and hospital-acquired infections, such as *Clostridioides difficile (C. difficile)*, meticillin-resistant *Staphylococcal aureus* (MRSA) vancomycin-resistant *Enterococcus* and postoperative surgical site infections.[4,13–15] Furthermore, PALs may delay administration of the first dose of antibiotic/s during the management of sepsis and PALs have also been linked to enhanced healthcare costs of the order of several million dollars due to use of alternative more expensive antibiotics, lengthened hospital stay, higher re-admission rates, morbidity and mortality.[4,16–19]

A summary of published evidence regarding the adverse impact of PALs on quality of care and healthcare costs:[1,4,13,15,19]

- poor AMS
- enhanced risk of AMR
- enhanced risk of hospital-acquired infections:
    - *C. difficile*
    - vancomycin-resistant *Enterococcus*
    - surgical site infections
    - MRSA

- greater use of Watch and Reserve group of antibiotics as per World Health Organization (WHO) AWaRe classification and reduced use of Access group of antibiotics
- higher hospital re-admission rates
- increased length of hospital stay (LOS)
- delay in institution of standard sepsis management and treatment of severe infections, for example, bacterial meningitis, streptococcal infections, bacterial pneumonia and gas gangrene
- higher mortality
- estimated costs: increased to the order of several million USD per year in the USA

Current standard of care

Current standard of care involves review by a specialist in allergy with a systematic clinical history, review of previous clinical and prescription records where relevant, skin testing, and a supervised penicillin oral challenge (if skin tests are negative), as per the British Society for Allergy and Clinical Immunology (BSACI) guidelines.[20] Oral penicillin challenge is the gold standard procedure to exclude an allergy and confirm clinical tolerance. Removal of PALs from clinical records after formal evaluation is termed penicillin allergy de-labelling.

There is an unmet need for allergy specialists in the UK NHS and in other countries and penicillin allergy tests are not routinely available.[21] This leads to prescription of less preferable broad-spectrum antibiotics, thereby increasing the risk of AMR.

The huge burden of PALs and unmet demand for allergy services are aggravated by the lack of routine access to penicillin allergy tests for inpatients and in primary care. Most hospitals in the NHS do not have a specialist allergy service and testing is available only to a very small proportion of patients with a PAL. There are BSACI criteria regarding referral for penicillin allergy tests, and this is restricted to patients with infection-related comorbidities, such as asplenia, immunodeficiency, bronchiectasis, diabetes, cancer, etc., where beta-lactam antibiotics are usually first choice antibiotics.[22]

Recent evidence regarding penicillin allergy de-labelling

Patients with a PAL may be stratified as 'low risk' and 'high risk' based on a structured clinical history, review of clinical records and comorbidities.[1,23–25] 'Low risk' patients are those where a true allergy or HSR is highly unlikely, and a direct oral penicillin challenge (DPC; without undertaking allergy skin tests) has been shown to be a safe and effective intervention when undertaken in a safe clinical environment by a non-allergy specialist.[26] Between 40% and 60% of patients are deemed 'low risk' based on this approach.[27–29]

Goldberg *et al.*, in 2008, recognised that many patients with a 'low-risk' allergy history have negative skin tests with the majority proceeding to an oral challenge test.[30] They reported regarding the safety of DPC in 'low risk' patients. Other groups later reported similar findings.[31,32] More recently, a randomised controlled trial comparing skin tests with challenge versus DPC in 'low-risk' patients demonstrated safety and efficacy of a DPC.[33] Skin testing has a poor positive predictive value, with false positives as a common clinical problem that limits its usefulness as a test in 'low-risk' patients.[33]

Direct oral penicillin challenge undertaken by non-allergy specialists in 'low risk' patients has become an accepted penicillin allergy de-labelling method in many countries.[26] A recent systematic review and meta-analysis reported successful de-labelling involving 5056 patients from 23 studies from around the world. Studies with and without undertaking skin tests prior to challenge were included.[9] A higher rate (97%) of de-labelling was noted in patients undergoing DPC, most likely related to their 'low risk' status, as opposed to the group who were offered prior skin tests (88% de-labelled), probably due to 'high risk' status in the latter.[9] Overall, 94% of patients were de-labelled.[9] Except for one case of interstitial nephritis, there were no serious type-I or type-IV HSRs.[9]

Another systematic review highlighted the feasibility and safety of DPC involving 1202 patients from 13 studies; 96.5% were de-labelled, and there were 3.5% immediate and non-immediate HSRs, all relatively mild.[34]

Antimicrobial resistance

Antimicrobial resistance is a global public health[35] concern and was highlighted as a high-priority area by the United Nations in a declaration in 2016. The UK has responded to this global campaign with a series of National Action Plans and national surveillance of AMR patterns with key aims around reduction of inappropriate antibiotic use, specifically broad-spectrum antibiotics [UK 5-year action plan for AMR 2019–24 – GOV.UK (www.gov.uk); accessed 1 May 2023]. Inappropriate antibiotic use drives AMR, with broader-spectrum antibiotics having a greater propensity compared to narrower-spectrum antibiotics.

The WHO categorised antibiotics into three broad groups [AWaRe; 2021 AWaRe classification (https://www.who.int/publications/i/item/2021-aware-classification); accessed 1 May 2023], Access (e.g. penicillins, sulphonamides, first-generation cephalosporins), Watch (e.g. second–fourth-generation cephalosporins, quinolones, imipenem/cilastin) and Reserve (fifth-generation cephalosporins, aztreonem, linezolid) based on their spectrum, anticipated risk of resistance development, risk of toxicity and clinical utility. In the UK, there is a national drive to align antibiotic prescribing practices with the 'Access' group. Most penicillins are in the Access group and constitute first-choice antibiotics for common infections. A recent systematic review reports a higher likelihood for antibiotics in the Watch and Reserve groups to drive the emergence of high-priority multidrug-resistant organisms, further supporting the ambition for health services to reduce the use of antibiotics from the Watch and Reserve groups in favour of the Access groups.[36,37] The UK 5-year AMR plan sets out an ambition to reduce non-Access antibiotic use (i.e. Watch and Reserve antibiotics) by 10% by 2024 from the baseline in 2017.[38]

Penicillin allergy labels: a risk factor for antimicrobial resistance

Penicillin allergy labels are common and result in the use of inappropriate antibiotics predominantly from the 'Watch' and 'Reserve' categories. Patients with a PAL are about four times more likely to receive an antibiotic in the non-Access antibiotic groups (i.e. Watch and Reserve) than those without.[39] However, after formal penicillin allergy testing, > 95% of patients with a PAL are able to tolerate penicillin, thereby facilitating greater use of 'Access' group of antibiotics. One study modelled the impact on inpatient antibiotic prescribing after removal of 90% of PALs and showed a reduction in non-Access antibiotic use by 10.4% and total antibiotic use by 1.56%, demonstrating the potential impact of penicillin allergy de-labelling to reduce broad-spectrum antibiotic use.[37] Inpatient real-world penicillin allergy de-labelling studies from the USA, Australia and New Zealand have demonstrated the impact of penicillin allergy de-labelling on reducing broad-spectrum antibiotic use with a corresponding increase noticed in narrower-spectrum penicillin antibiotic use.

Removal of inaccurate PALs, through allergy tests, therefore, has the potential to significantly improve AMS, in line with WHO and UK ambitions, and to reduce healthcare costs and improve clinical outcomes. The paucity of allergists has led non-allergists to explore the feasibility of penicillin allergy de-labelling employing DPC in low-risk patients and a recent systematic review has demonstrated the safety and effectiveness of penicillin allergy de-labelling delivered by non-allergy trained doctors, nurses and pharmacists, amongst others, with increases in penicillin antibiotic use and a concurrent reduction in broader-spectrum antibiotic use.[26,34] The majority of the studies included in the systematic review are from USA, Australia and New Zealand health systems with very limited European data, with only one relatively small study from England in a presurgical setting and an inpatient study from Scotland.[26,34]

In 2022, the BSACI[40] published guidelines on non-allergist penicillin allergy de-labelling. These guidelines recommend a risk stratification approach and DPC for de-labelling 'low risk' patients in an appropriate safe clinical environment supported by a robust local clinical governance framework. The methodology employed in the SPACE study aligns with the BSACI guideline.[40]

Justification of research

The penicillin allergy de-labelling patient pathway is a complex intervention for inpatients and the views and perspectives of patients and healthcare workers, specifically non-allergy specialists have hitherto not been explored in the NHS. Wilson *et al*. conducted a telephone survey to explore patient acceptability of penicillin allergy de-labelling in an Australian study.[41] Patients reported feeling safe during testing and would recommend the intervention to others. However, there were patients who had tested negative but continued to avoid penicillin post-testing with some still considering themselves to be allergic.[41] A review undertaken by Wanat *et al.* explored patient and prescribers' views of penicillin allergy testing and subsequent antibiotic use.[42] Several patients and clinicians remained reluctant to consume or prescribe penicillin antibiotics after a negative penicillin allergy test, probably due to a lack of confidence in and awareness of penicillin allergy testing. In the UK, Wanat *et al.* explored primary care patients' views of penicillin allergy de-labelling and reported that patients were unaware of the benefits of penicillin allergy de-labelling but those who had experienced negative consequences of PAL were motivated to get tested.[43] Clinicians reported that they felt testing could be beneficial to patients but had limited experience with allergy services.[43]

A summary of possible reasons for inaccurate PALs:[11,43,44]

1. suboptimal knowledge of basic concepts of drug allergy amongst HCPs
2. mis-labelling patients as a penicillin allergy – non-immune side effects, infection-related rash, childhood viral infections
3. lack of confidence amongst HCPs to avoid attachment of a PAL
4. communication challenges in health care, for example, primary and secondary care interface
5. lack of awareness amongst patients, for example, avoiding penicillin due to family history
6. re-labelling with a PAL post de-labelling

The opportunity for penicillin allergy de-labelling services led by non-allergists and its acceptability to patients and HCPs are largely unknown in the UK context. There are important gaps in our understanding of some highly relevant areas relating to this model. Further insight is required into the following:

1. behaviour/perceptions of patients and HCPs in secondary care regarding this approach
2. time and resources required to support the process
3. views of senior management in secondary care

Study objectives

Primary

- To explore behaviour, attitudes and acceptability of patients, HCPs and managers regarding the use of DPC in 'low risk' patients.
- To develop treatment pathways and a clinical governance framework for this service model.

Secondary

- To assess the proportion of 'low risk' patients with PAL who would be eligible for a DPC.
- To assess the proportion of 'low risk' patients who would be willing and complete a DPC.
- To explore practical aspects of implementing this penicillin allergy de-labelling programme in secondary care by investigating factors, such as organisational context, treatment pathway, protocol implementation, time taken and resources.
- To evaluate the potential cost-effectiveness of this service model.

Outcomes

Primary

- Describe the facilitators and barriers of using DPC in de-labelling 'low risk' patients with a PAL.
- Development of penicillin allergy de-labelling pathway and a 'fit for purpose' governance framework that can be rolled out to NHS Trusts.

Secondary

- Percentage stratified as 'low risk' and 'high risk'.
- Percentage of 'low risk' patients willing to undergo DPC.
- Percentage of 'low risk' patients safely negotiating DPC.
- Description of adverse events (AEs).
- Development of 'fit for purpose' information technology (IT) systems and cascading allergy status to primary care.
- Clinical governance framework including leadership and defining roles for membership of multidisciplinary team.
- Audit tools.
- Health economic modelling to explore cost-effectiveness and help in strategic planning for hospital managers.

Study clinical settings and workstreams

This study involved three clinical settings including inpatients in acute medical/infectious diseases unit (AMU/IDU), and outpatients involving presurgical and haematology-oncology units across three acute care Trusts [University Hospitals Birmingham NHS Foundation Trust (UHB), Oxford University Hospitals NHS Foundation Trust, and Leeds Teaching Hospitals]. The inclusion of acute and elective clinical care settings in this study allowed us to study enablers and barriers to penicillin allergy de-labelling by a non-allergy specialist HCP in a very busy with rapid turnover of patients and relatively less busy clinical environment.

This research involved three workstreams (WSs) spanning 24 months (1 May 2021–30 April 2023) and employed a mixed-methods approach with a combination of qualitative and quantitative methodology. Broadly, the WSs are summarised as follows:

Workstream 1: Patients with a PAL were screened and those interested and deemed potentially suitable were stratified into 'low risk' and high risk' as per study protocol by a trained research nurse (RN) or a trained research pharmacist (RP). 'Low risk' patients underwent DPC.

Workstream 2: One-to-one semistructured interviews with patients and focus group sessions with prescribers, relevant HCPs, clinical leaders and managers were conducted at each site.

Workstream 3: Care pathway mapping was conducted at each site and decision-analytic modelling carried out to determine the potential cost-effectiveness of DPC.

Ethics Committee approval

This study was approved by the London Bridge Ethics Committee (REC Reference 21/PR/0814; IRAS project ID: 293544) on 23 July 2021. Principles of Good Clinical Practice were carefully followed during the study at all participating sites. Specifically, patients were provided with the patient information sheet and any questions and concerns were addressed by the research team prior to obtaining informed consent.

Patient and public involvement and engagement

Patient and public involvement and engagement (PPIE) in the SPACE study included Allergy UK (Mrs Amena Warner, Clinical lead), the UK Sepsis Trust (Dr Ron Daniels, CEO) and members of the public. PPIE input was considered at every stage of the study including preparation of grant application, study protocol (and amendments), patient information leaflet, recruitment strategy, sharing and input in data analysis from a patient/public perspective and dissemination process. Recommendations from the PPIE group were duly considered and implemented across all participating sites. Our approach was in keeping with Guidance for Reporting Involvement of Patient and the Public2 (GRIPP2) guidance/checklist.[45]

At a very early stage, patients with a lived experience of PAL suggested that it is important to raise public awareness of the adverse impact of inaccurate PALs via multiple streams including posters and information leaflets in general practice surgeries. PPIE input and learning from the Penicillin Allergy De-labelling ahead of Elective Surgery study,[8] the Drug Allergy Labels in Elective Surgical Patients (DALES) study[46] and the [Allergy Antibiotics and Microbial Resistance (ALABAMA) study; www.phc.ox.ac.uk/research/participate/alabama-trial; accessed 2 February 2023], was also applied to the SPACE study proposal, for example, development of the patient information leaflet.

The representatives from patient organisations, Allergy UK (Mrs Amena Warner) and the UK Sepsis Trust (Dr Ron Daniels) contributed to the design of the SPACE study proposal. In addition, the PPIE research team at UHB provided guidance in preparation of the PPIE section of the grant application and in the establishment of PPIE groups for the study.

Establishment of patient and public involvement and engagement groups for the SPACE study

At each site, the plan was to recruit three groups of five people through an open invitation. An open invitation for recruitment to the PPIE group was hosted on the University of Birmingham website, the SPACE study twitter account and disseminated via the UHB chaplaincy services. Applications were assessed to ensure diversity with respect to age, gender and ethnicity by the SPACE study investigators. Shortlisted applicants were asked if they had any preference for the centres in the study. During the allocation of PPIE members to each study site, we ensured that that each group had an adequate skill mix with respect to research experience. UHB and Oxford had one PPIE group comprising five members. Due to some logistic constraints, it was not possible to establish a similar group at Leeds, and National Institute for Health and Care Research (NIHR) was notified. At each site, local investigators coordinated meetings with their respective PPIE groups and maintained regular contact. The membership agreed on terms of reference and received copies of meeting agenda, minutes and ongoing study progress updates and NIHR reports. All meetings were conducted via a virtual platform. Two patients with lived experience at Leeds, who had previously confirmed their participation in an advisory capacity, were allocated to other studies and therefore were unable to support the SPACE study. PPIE input was sought for all WSs of the SPACE study.

Patient and public involvement and engagement membership activity in Birmingham and Oxford

The study teams in Birmingham and Oxford met with their respective PPIE group five times during the course of the study. An agenda and meeting papers were circulated to the PPIE group ahead of each meeting. NIHR progress reports and important study updates, including proposed amendments were shared with the PPIE group for their views, perspectives and feedback was carefully considered.

At the first meeting, the principal investigator (PI) from Oxford and Birmingham delivered a presentation to introduce the study to the membership. The benefits of de-labelling within each clinical setting in the study were highlighted, including in the context of 'therapeutic de-labelling' (described in *Chapter 2*) ensuring there was no researcher bias, as far as possible.

The Birmingham PPIE group sought clarification regarding the informed consent process in the AMU setting, as this is a busy environment involving unwell patients. The PPIE group felt that patients might potentially feel pressured into giving informed consent within this setting. The Oxford PPIE group was content with the patient information sheet; however, they sought reassurance that patients would be given sufficient time to consider and discuss the study with other HCPs prior to participation. The study team considered this feedback carefully and reassured the group that

informed consent would only be obtained when patients felt that they had adequate time to consider participation and after all their concerns had been addressed by the study team. The PPIE membership felt re-assured about the consent process and later supported the study protocol amendment to offer all patients on AMU 1 hour as a minimum time to obtain informed consent.

The study team and the PPIE membership worked collaboratively to develop strategies to enhance recruitment amidst the coronavirus disease 19 (COVID-19) pandemic. The PPIE membership suggested that Oxford and Leeds review the recruitment strategy adopted in Birmingham, as recruitment was relatively slow at these sites. The Birmingham site shared its study set-up and recruitment strategy within each clinical setting with Oxford and Leeds after these sites were open to recruitment. As the study progressed, each site developed its own recruitment strategy due to the differences in patient demographics and other local factors at each site.

All study protocol amendments were discussed with the PPIE membership. Specifically, the PPIE membership supported an important amendment relating to the reduction in DPC sample size from 375 to 122 (described in *Chapter 2* and further details in *Report Supplementary Material 1* under study amendments). They were in agreement that this would not compromise study objectives and would generate valuable data for the NHS with respect to the establishment of strategies to address inaccurate PALs.

Progress with patient uptake for WS2 interviews was slow at the start of the study. The PPIE group were consulted regarding the best possible approach to recruitment. They suggested encouraging patients to participate in WS2 interviews by pre-arranging dates and time slots for interviews at the point of informed consent. This led to an immediate increase in the conversion rates with respect to those who consented to participate in WS1 followed by completing interviews in WS2.

For WS3, the PPIE membership were consulted for their opinions regarding data extraction for developing an economic model for DPC. The investigators wanted to ensure that the proposed data extraction for the health economics evaluation was in keeping with regulatory approvals and research governance. The PPIE membership was supportive of the proposed approach and advised the study team to seek further advice and confirmation from the sponsor research governance department.

The Birmingham PPIE membership was also consulted regarding the dissemination strategy. Professor Iestyn Williams (co-lead for WS2 and SPACE study lead for dissemination) summarised the strategy. The membership was keen to contribute to the lay summary infographics of study findings and to facilitate dissemination via their networks. In addition, the PPIE group also agreed to provide input into patient-level documents, multimodality learning resources, social media, and dissemination through charities and third-sector groups. The UK Sepsis Trust and Allergy UK also agreed to contribute to the dissemination process.

Chapter 2 A multicentre study to investigate the role for a direct oral penicillin challenge in 'low risk' patients with a penicillin allergy label

BOX 2 Key messages

- There was a very high uptake (81%) of direct oral penicillin challenge amongst consented low-risk patients.
- Ninety-seven per cent of patients who underwent the challenge were de-labelled.
- There were no serious type-I or type-IV hypersensitivity reactions across the three participating sites.
- Penicillin allergy de-labelling employing a direct oral penicillin challenge can be delivered by non-allergy specialists with appropriate training and governance framework in place.
- Opportunistic de-labelling in an elective setting may offer greater opportunities for tackling inaccurate penicillin allergy labels.
- Inpatient de-labelling may be better suited for selected patients in the context of therapeutic de-labelling for concurrent bacterial infections.
- The conversion rate from screening > consent in the study pathway was modest (12%).
- Multipronged strategies are needed to enhance opportunities for penicillin allergy de-labelling including raising awareness amongst patients and HCPs creating mechanisms to contact patients at an optimal time point that suits their personal circumstances and clinical suitability and stability, governance framework for those who do not have the capacity to consent and culturally tailored supportive measures for those from ethnic minority groups.

Introduction

A DPC involves supervised administration of penicillin antibiotics without undertaking allergy skin tests to patients stratified as 'low risk' (i.e. highly unlikely to have an immune-mediated reaction).[1] This intervention has been shown to be safe and feasible in 'low risk' patients, particularly in the USA, Australia and New Zealand and has been successfully delivered by non-specialist HCPs.[17,34,48] Given the differences in patient pathways and health service framework between countries, it is important to test the feasibility of delivering DPC in the routine NHS setting.

Aim

The main aim of this WS was to investigate the feasibility of DPC in inpatient and outpatient settings across three participating centres in England and generate relevant data regarding patient demographics, risk stratification, clinical characteristics and outcome.

Objectives

1. To provide a demographic description of PALs in AMU/IDU units, haematology-oncology units and presurgical units.
2. To determine conversion rates from screening of participants to informed consent and enumerate reasons for failure to progress.
3. To determine the mean time taken to complete screening and risk stratification.
4. To determine the proportion of consented patients stratified as 'low risk' and 'high risk'.
5. To provide a descriptive analysis of DPC uptake and outcomes amongst 'low risk' patients.
6. To determine the proportion of 'high risk' patients meeting national criteria for a referral to an allergy specialist for penicillin allergy tests.

Study design

This was a prospective multicentre observational study conducted at the following sites over 24 months:

- UHB
- Oxford University Hospitals NHS Foundation Trust
- Leeds Teaching Hospitals NHS Trust.

The study involved patients in three clinical settings at each site including:

- AMU and IDU.
- Haematology-oncology unit.
- Presurgical assessment unit.

This study involved two main stages based on predetermined study criteria for each stage:

- Screening for potential suitability.
- Invitation to participate, provision of patient information leaflet, informed consent and risk stratification.

Screening criteria

Inclusion criteria

Patients with a current PAL, ≥ 18 years, with the capacity to give informed consent.

Exclusion criteria

- Clinically unstable patients, that is unstable cardiorespiratory status (e.g. respiratory failure, cardiac failure, pre-hepatic encephalopathy etc.).
- History of serious non-immediate systemic HSRs to penicillin.
  - Documented Steven–Johnson syndrome, toxic epidermal necrolysis (TENS), acute exanthematous generalised pustulosis, erythema multiforme, haemolytic anaemia, vasculitis, acute interstitial nephritis

- Those deemed unsuitable for medical reasons (unlikely to comply with study protocol).
- Pregnant.
- Breastfeeding.
- Concomitant COVID-19 infection.
- Those participating in any other research currently or those who have participated in research involving medicinal products, medical devices and/or other interventions in the preceding 6 weeks.
- Patients currently receiving omalizumab or those who have received omalizumab within 6 months prior to proposed DPC.
- Patients currently taking antihistamines and unable to temporarily withdraw for the proposed DPC.

Those deemed potentially suitable progressed to the next stage.

Patient identification and recruitment, risk stratification, direct oral penicillin challenge and data analysis

Acute medical unit

Patient identification for participation

A list of inpatients with PALs was generated from the respective Trust electronic prescribing (EP) systems (or other information systems available at study sites) on a daily basis and patients were screened to determine eligibility for

potential inclusion for risk stratification. This process was conducted by the RN/RP in liaison with respective clinical teams. Screening was carried out using a standardised proforma (see *Report Supplementary Material 1*), Monday–Friday (excluding bank holidays) during working hours (8 a.m.–5 p.m.).

Informed consent and risk stratification

After seeking permission from the respective clinical care team, the RN/RP approached patients with a patient information sheet. A minimum period of 4–6 hours was given to consider participation. Patients were also given an option to take additional time for consideration as needed. In those patients where the clinical care team identified an urgent need for the administration of a penicillin antibiotic and/or in those who were keen to participate, informed consent was sought within an hour after the patient information sheet was issued.

Informed consent was obtained by a RN/RP prior to a systematic risk stratification process as per pre-determined criteria using a standardised study proforma (see *Report Supplementary Material 1*). This was conducted by trained RPs in Oxford and Birmingham sites and trained RNs at Leeds. A nominated study consultant, with no background in allergy or immunology provided clinical support to the RP/RN.

Presurgical and haematology-oncology units

A list of patients with PALs was generated from the Trust EP system (or other information systems available at study sites) by the RN/RP and patients were screened as described above. For those attending face-to-face consultations, a patient information sheet was issued during the appointment. For patients undergoing virtual consultations, the RN/RP contacted patients directly by telephone to introduce the study and seek permission to forward the patient information sheet by post and/or e-mail. The patient was advised to contact the research team directly or inform their clinical care team to express interest in participation or, alternatively, permission was sought from the patient for the research team to contact them via telephone after 48 hours to check if they wish to participate. Informed consent was obtained prior to risk stratification. The risk stratification outcome was approved by the study consultant.

Risk stratification process

This was conducted using a standardised proforma (see *Report Supplementary Material 1*) and criteria and included a review of previous prescription and health records or/and a phone call to the patient's general practice (GP) surgery for additional clarification as deemed necessary. Patients were stratified as 'low risk' and 'high risk'. The risk stratification criteria as listed are as follows:

Low risk: Those with one or more of the following:

- history of nonspecific symptoms *only* (e.g. headache, isolated dizziness, gastrointestinal symptoms)
- thrush *only*, no other symptoms
- mild 'benign' rash
- history of 'childhood rash – no further details available'
- pruritus without rash
- gaps in clinical history, but clearly suggestive of a non-life-threatening reaction and did not require hospitalisation
- remote (> 10 years) reactions without features of an IgE-mediated reaction
- tolerated treatment with amoxicillin/co-amoxiclav since registration of PAL
- no history of an 'index episode' but advised to avoid penicillins due to family history.

#benign rash: Check list for a 'benign' rash is summarised as follows:

- non-blistering, not painful, non-desquamating, non-bruising
- no associated mouth ulcers/genital ulcers
- not systemically unwell due to the reaction
- not hospitalised.

If any of the above criteria were not met or relevant information was not available, the patient was stratified as 'high risk'.

High risk: Those with any one or more of the following:

- severe, uncontrolled or brittle asthma
- severe chronic obstructive pulmonary disease (COPD)
- heart failure or severe impairment in cardiac function
- symptoms suggestive of an IgE-mediated reaction or anaphylaxis after administration of penicillins
- blistering, painful, desquamating or bruising rash
- symptoms requiring hospital admission
- history of angioedema as a part of index reaction.

Those classified as 'low risk' were invited to participate in a DPC. The risk stratification status was reconfirmed prior to DPC to ensure patients' clinical status had not changed in the interim.

Direct oral penicillin challenge procedure

This was conducted in a safe clinical environment under the clinical supervision of a study consultant and with immediate access to cardiopulmonary resuscitation. A standardised proforma (see *Report Supplementary Material 1*) was used to capture data.

The steps employed for DPC are listed as follows:

1. The research team confirmed that antihistamines had not been taken during the 3 days prior to the DPC.
2. A urine pregnancy test was performed for female participants of child-bearing potential prior to commencing the DPC.
3. Baseline vital parameters including heart rate, blood pressure, and SpO_2 were checked.
4. Oral amoxicillin 500 mg was administered.
5. Patients were monitored for signs and symptoms of an allergic reaction for 60 minutes following DPC and vital parameters were repeated.
6. This was followed by 'opportunistic' or therapeutic' de-labelling.

Therapeutic de-labelling involved a full therapeutic course of appropriate penicillin antibiotics as deemed necessary by their respective clinical team to treat any intercurrent infection after exclusion of type-I HSR.

Opportunistic de-labelling involved a modest dose of 250 mg twice daily for 3 days following exclusion of type-I HSR. This was conducted to account for the following clinical scenarios:

1. temporal association was unclear from clinical history with respect to index reaction/s
2. index reaction/s was delayed in onset, that is not after the first dose but occurred during a course of therapy (e.g. day 2 or day 4 of treatment).

For inpatients who commenced opportunistic de-labelling and then developed an intercurrent infection that required a full therapeutic course of amoxicillin or an alternative penicillin-based antibiotic, treatment was switched to an appropriate regimen following discussion between the research team and respective clinical teams. The modest dose (250 mg) of amoxicillin used for opportunistic de-labelling was withdrawn/amended at this stage.

Follow-up

- Patients were provided with a 'participant note' and counselled prior to discharge and provided with written guidance regarding seeking urgent medical attention or calling their GP if needed. In those who temporarily withdrew antihistamines for the DPC, specific advice was provided by the research team regarding the recommencement of antihistamines following completion of DPC.
- All patients were either reviewed (if they are still an inpatient) or contacted via telephone or virtual platform on day 5 to establish clinical tolerance and exclude a type-IV HSR. Patients were contacted by the research team on the next working day, if day 5 follow-up call fell on a weekend or a national bank holiday and this was recorded in study

documentation retrospectively. Patients were advised to contact the research team in case they developed delayed-onset symptoms either before or after day 5.

De-labelling and communication with patient and general practitioner

1. The outcome of the DPC was discussed with the patient, communicated in writing to their GP and hospital records were updated accordingly.
2. For the 'high risk' group and those declining DPC, the outcome of risk stratification was communicated in writing to their GP.

Data analysis

Sample size

Original total sample size for DPCs was 375. This was revisited and revised in light of low conversion rates from screening to consent process across the three participating sites during the first 3–4 months of the study.

Revised sample size calculation

A recent systematic review[34] involving 1202 patients in 13 studies (inpatient and outpatient 'low risk' with a PAL) reported ~97% de-labelling and there were no severe adverse reactions related to DPC. To estimate this rate with a 95% confidence interval (± 3%), a total number of at least 122 DPCs were required across the 3 participating sites.

Statistical methodology

Data were entered on Research Electronic Data Capture (REDCap). Tables were constructed by collating data from each patient and cross-tabulating patient characteristics against hospital and clinical settings. To aid in the detection of potential associations, continuous variables (age) were compared between the hospital/clinical setting groups using Kruskal–Wallis tests. This was for a guide only and was not intended as a definitive test. Similarly, categorical variables (gender) were compared across hospital/clinical settings groups using Pearson chi-squared tests, again for guidance only.

More detailed analysis was provided to compare outcomes, such as de-labelled 'Yes'/'No', with the use of logistic regression. First, the outcome was regressed upon each potential 'risk factor', such as gender, producing an unadjusted odds ratio (OR; by exponentiation of the fitted parameter), and then a multivariable logistic regression was used to yield adjusted ORs. Once again, given the observational nature of the data, and since perfect adjustment cannot be guaranteed, the resultant ORs are intended to summarise the observed potential effects and not be interpreted as definitive tests of association.

Study amendments

As stated above, we had set out to conduct 375 DPCs initially but revisited overall sample size after reviewing study recruitment rate across the three sites after the first 3–4 months. Given that our primary study objective was not to investigate safety of DPCs, sample size was re-calculated (revised to 122). This amendment received support from our oversight committees and was approved by NIHR. This is summarised alongside other study amendments in *Report Supplementary Material 1*.

Results

A study flow diagram is shown in *Figure 1*.

Patients

Screening

A total of 2257 patients (males = 834; females = 1423) with a PAL were identified for screening across the 3 participating sites. This included 795, 990 and 472 from Birmingham, Leeds and Oxford, respectively. From a clinical setting perspective, 900, 365 and 992 patients with a PAL were identified at AMU/IDU, haematology-oncology

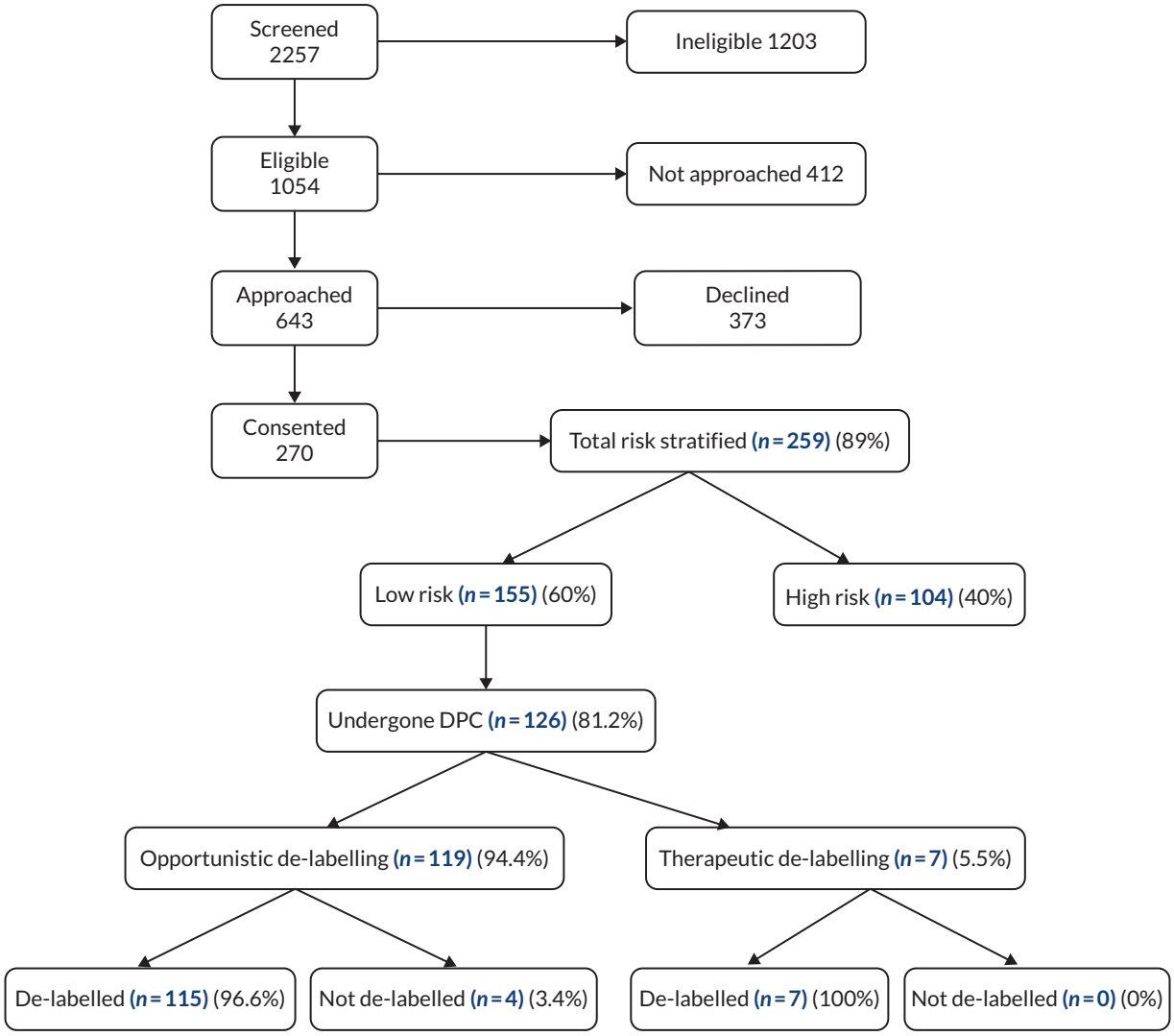

FIGURE 1 Study flow diagram. Reproduced with permission from Krishna *et al.*[47] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The figure includes minor additions and formatting changes to the original text.

and presurgical units, respectively. Age was captured as 'age brackets' as per regulatory approval at screening and is summarised alongside other demographic variables in *Table 1*. Following screening process as per study proforma, 1203 patients were deemed ineligible to proceed further in the study pathway, and 1054 were eligible. Four hundred and twelve out of the 1054 patients could not be approached due to one or more logistical reasons such as the patient being discharged, moved to another location, not being able to reach the patient by phone or the research team not being able to contact the patient. Six hundred and forty-three patients were approached by the research team and 373 declined to participate.

Out of the total screened sample of 2257, ethnicity data were available for 1972 (87.4%) and not available for 286 (12.6%) patients. There were 100 (16%), 64 (7.2%) and 97 (20.1%) patients of non-white ethnicity screened with a PAL at Birmingham, Leeds and Oxford, respectively. Overall, the screened study sample included 11.6% patients of non-white ethnicity.

Consent

Six hundred and thirty-four patients were approached to participate in the study across the 3 sites and 270 (42%) consented. One hundred and two, 91 and 77 patients consented from Birmingham, Leeds and Oxford, respectively. From a clinical setting perspective, 30, 45 and 195 patients consented from AMU/IDU, haematology-oncology and

TABLE 1 Regression analysis of patients deemed eligible at screening (dependent – eligible)

	Not eligible *n* (%)	Eligible *n* (%)	OR (univariable)	OR (multivariable)
Hospital				
Birmingham	422 (53.1)	373 (46.9)		
Oxford	239 (50.6)	233 (49.4)	1.11 (0.88–1.39, $p = 0.388$)	1.93 (1.46–2.55, $p < 0.001$)
Leeds	541 (54.6)	449 (45.4)	0.94 (0.78–1.13, $p = 0.526$)	1.65 (1.31–2.08, $p < 0.001$)
Clinical setting				
AMU/IDU	732 (81.3)	168 (18.7)		
Presurgical	292 (29.4)	700 (70.6)	10.45 (8.43–13.00, $p < 0.001$)	9.51 (7.56–12.03, $p < 0.001$)
Haematology-oncology	178 (48.8)	187 (51.2)	4.58 (3.52–5.97, $p < 0.001$)	5.16 (3.84–6.96, $p < 0.001$)
Age range (years)				
< 30	44 (41.9)			
30–39	60 (39.7)	91 (60.3)	1.09 (0.66–1.82, $p = 0.728$)	0.80 (0.45–1.41, $p = 0.437$)
40–49	97 (37.9)	159 (62.1)	1.18 (0.74–1.88, $p = 0.478$)	0.98 (0.58–1.65, $p = 0.933$)
50–59	150 (42.9)	200 (57.1)	0.96 (0.62–1.49, $p = 0.863$)	0.77 (0.47–1.27, $p = 0.312$)
60–69	192 (47.4)	213 (52.6)	0.80 (0.52–1.23, $p = 0.314$)	0.69 (0.42–1.13, $p = 0.141$)
70–79	283 (56.3)	220 (43.7)	0.56 (0.36–0.86, $p = 0.008$)	0.58 (0.35–0.94, $p = 0028$)
≥ 80	376 (77.2)	111 (22.8)	0.21 (0.14–0.33, $p < 0.001$)	0.36 (0.22–0.59, $p < 0.001$)
Gender				
Male	432 (51.8)	402 (48.2)		
Female	770 (54.1)	653 (45.9)	0.91 (0.77–1.08, $p = 0.288$)	0.94 (0.77–1.15, $p = 0.547$)

presurgical units, respectively. There were 154 female and 116 male participants. Detailed centre-wise and clinical setting-wise demographics are summarised in *Table 2*.

Conversion rates and regression analysis

Overall conversion rate (screening > consent) across all study sites and clinical settings was relatively low at 12% (*Figure 2*). This was 13%, 9% and 16% at Birmingham, Leeds and Oxford, respectively. The overall conversion rate in an acute setting was very low at 3.3% and relatively higher in haematology-oncology (12.3%) and presurgical (19.7%) settings. The combined conversion rate in an elective setting was 17.7%. These data are summarised in *Tables 3–5*.

Reasons for failure to progress from screening to consent stage

Amongst 1203 patients deemed ineligible at screening, there were one or more reasons for their failure to progress (see *Figure 2*). These included pregnancy/breastfeeding ($N = 7$), no identifiable PALs for confirmation in patient records upon further scrutiny ($N = 21$), serious systemic delayed HSR, such as Steven–Johnson syndrome ($N = 44$), TENS, etc., COVID-19 infection ($N = 92$), lack of capacity to consent ($N = 266$), underlying psychiatric/psychological illness ($N = 337$), currently participating in another research study ($N = 70$), clinically unstable ($N = 440$), omalizumab therapy ($N = 2$) and/or medically deemed unsuitable ($N = 413$).

Univariable and multivariable regression analysis

Regression analysis was conducted to determine if there were centre-wise and clinical setting-wise factors influencing eligibility to progress from screening to eligibility to participate (see *Tables 1*, *3–5*). Progression in the study pathway

TABLE 2 Demographics of consented patients

	ALL			AMU/IDU			Presurgical			Haematology-oncology		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	102	77	91	10	17	3	61	51	83	31	9	5
Age years [median (IQR)]	60.00 (51.50–69.75)	58.00 (46.00–68.25)	61.00 (48.00–73.00)	65.00 (59.50–75.75)	53.00 (39.00–69.00)	55.00 (55.00–67.00)	59.00 (52.00–70.50)	56.50 (45.75–64.50)	61.00 (48.00–73.00)	58.00 (48.00–68.00)	63.00 (59.00–70.00)	63.00 (57.00–69.00)
Gender												
M (%)	41 (40)	32 (42)	43 (47)	4 (40)	7 (41)	1 (33)	19 (31)	20 (39)	38 (46)	18 (58)	5 (56)	4 (80)
F (%)	61 (60)	45 (58)	48 (53)	6 (60)	10 (59)	2 (67)	42 (69)	31 (61)	45 (54)	13 (42)	4 (44)	1 (20)
Ethnicity												
White (%)	62 (61)	61 (79)	80 (88)	7 (70)	16 (94)	2 (67)	40 (66)	38 (75)	73 (88)	15 (48)	7 (78)	5 (100)
Non-white (%)	10 (10)	16 (21)	5 (6)	1 (10)	1 (6)	0 (0)	6 (10)	13 (26)	5 (6)	3 (10)	2 (22)	0 (0)
Not recorded (%)	30 (29)	0 (0)	6 (7)	2 (20)	0 (0)	1 (33)	15 (25)	0 (0)	5 (6)	13 (42)	0 (0)	0 (0)

IQR, interquartile range. Reproduced with permission from Krishna *et al.*[47] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The table includes minor additions and formatting changes to the original text.

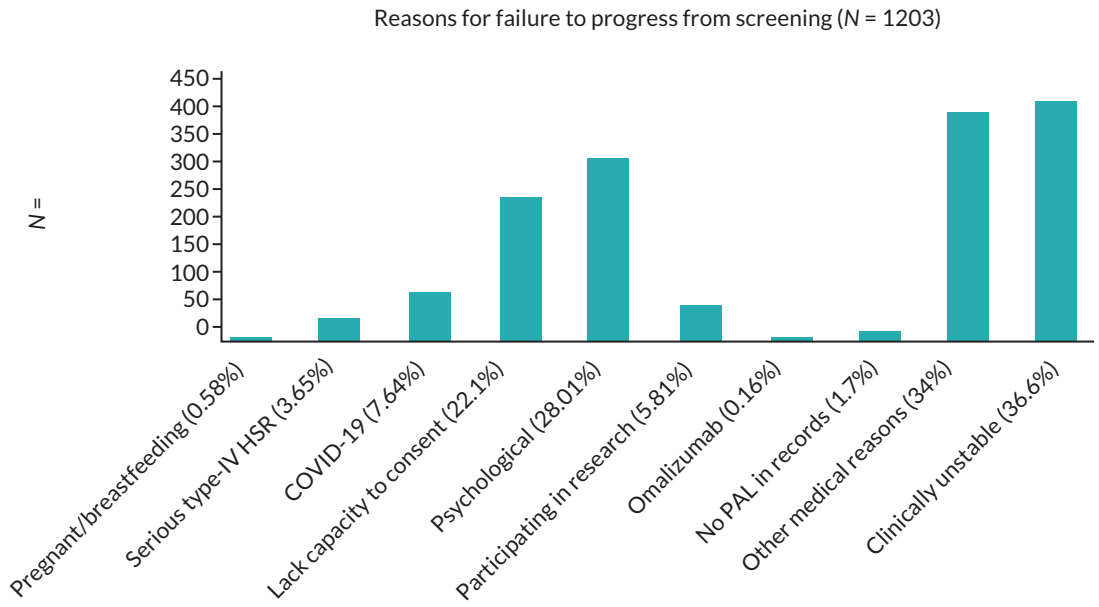

FIGURE 2 Reasons for failure to progress. Reproduced with permission from Krishna *et al.*[47] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The figure includes minor formatting changes to the original text.

significantly was greater in Oxford (OR −2.06; $p = 0.001$), less in Leeds (OR −0.37; $p < 0.001$), and greater in elective settings including haematology-oncology (OR −2.20; $p < 0.002$) and presurgical (OR −3.55; $p < 0.001$). Male patients (OR −1.36; $p = 0.02$), those at Oxford (OR −1.73; $p = 0.002$), haematology-oncology (OR −3.30; $p < 0.001$) and presurgical (OR −5.51; $p < 0.001$) were significantly more likely and those ≥ 80 years (OR −0.23; $p = 0.001$) significantly less likely to consent.

Risk stratification

Two hundred and fifty-nine patients out of 270 (96%) consented patients were risk stratified. Eleven patients could not undergo the stratification process due to practical reasons, such as changes in their circumstances and not being able to reach them despite multiple attempts. One hundred and fifty-five (60%) and 104 (40%) patients were stratified as 'low risk' and 'high risk', respectively. There were 60, 52 and 43 'low risk' patients at Birmingham, Oxford and Leeds, respectively, and these differences were not significant. There were 33, 46 and 25 'high risk' patients in Birmingham, Leeds and Oxford, respectively. A detailed summary of risk stratification is shown in *Tables 6* and *7*.

Direct oral penicillin challenge

One hundred and twenty-six out of 155 (81%) 'low risk' patients agreed to undergo DPC. We conducted four additional DPCs, as we wanted to deliver the DPC to all participants who had consented to participate and were deemed 'low risk' upon risk stratification. This was supported by our PPIE groups and sponsors. Of the 126 DPCs conducted, 7 (5.5%) and 119 (94.4%) respectively were 'therapeutic' and 'opportunistic' de-labelling. All patients who underwent therapeutic de-labelling were successfully de-labelled, and 115 out 119 patients (96.6%) who underwent 'opportunistic' de-labelling were successfully de-labelled. Overall, 122 out of 126 patients (97%) were de-labelled. One patient could not tolerate amoxicillin due to gastrointestinal side effects and did not complete the 3-day course. There was no evidence of type-I HSR in any patient while three patients developed a mild delayed–onset benign rash.

There were no cases of serious type-I or type-IV HSRs. There were two serious adverse events (SAEs) reported, one at Birmingham and another at Oxford, both deemed 'unlikely to be related to DPC'. These two SAEs were subjected to a detailed review by the SPACE team investigators, respective clinical care teams, the study sponsor's research development and innovation department and oversight committee Chairs and there was agreement this was not related to DPC.

Direct oral penicillin challenge data are summarised in *Table 8* and AEs and SAEs are summarised in *Tables 9* and *10*.

TABLE 3 Regression analysis of patients approached after establishing eligibility at screening

Dependent: approached				
	Not approached, *n* (%)	Approached, *n* (%)	OR (univariable)	OR (multivariable)
Hospital				
Birmingham	117 (31.4)	256 (68.6)		
Oxford	51 (21.9)	182 (78.1)	1.63 (1.12–2.40, $p = 0.012$)	2.06 (1.36–3.15, $p = 0.001$)
Leeds	244 (54.3)	205 (45.7)	0.38 (0.29–0.51, $p < 0.001$)	0.37 (0.27–0.51, $p < 0.001$)
Clinical setting				
AMU/IDU	101 (60.1)	67 (39.3)		
Presurgical	240 (34.3)	460 (65.7)	2.89 (2.05–4.10, $p < 0.001$)	3.55 (2.41–5.29, $p < 0.001$)
Haematology-oncology	71 (38.0)	116 (62.0)	2.46 (1.61–3.79, $p < 0.001$)	2.20 (1.35–3.60, $p < 0.002$)
Age range (years)				
< 30	24 (39.3)	37 (60.7)		
30–39	30 (33.0)	61 (67.0)	1.32 (0.67–2.59, $p = 0.421$)	1.48 (0.72–3.04, $p = 0.291$)
40–49	67 (42.1)	92 (57.9)	0.89 (0.48–1.62, $p = 0.706$)	1.02 (0.53–1.94, $p = 0.949$)
50–59	74 (37.0)	126 (63.0)	1.10 (0.61–1.98, $p = 0.741$)	1.35 (0.71–2.53, $p = 0.352$)
60–69	76 (35.7)	137 (64.3)	1.17 (0.65–2.09, $p = 0.600$)	1.55 (0.82–2.90, $p = 0.171$)
70–79	83 (37.7)	137 (62.3)	1.07 (0.59–1.91, $p = 0.818$)	1.57 (0.84–2.93, $p = 0.157$)
≥ 80	58 (52.3)	53 (47.7)	0.59 (0.31–1.11, $p = 0.106$)	0.99 (0.50–1.97, $p = 0.986$)
Gender				
Male	164 (40.8)	238 (59.2)		
Female	248 (38.0)	405 (62.0)	1.13 (0.87–1.45, $p = 0.362$)	1.10 (0.84–1.45, $p = 0.491$)

TABLE 4 Regression analysis of location of consented patients (centre-wise, clinical setting-wise and gender)

Dependent: consented				
	Not consented	Consented	OR (univariable)	OR (multivariable)
Hospital				
Birmingham	694 (87.2)	102 (12.8)		
Leeds	899 (90.8)	91 (9.2)	0.69 (0.51–0.93, $p = 0.015$)	0.86 (0.62–1.18, $p = 0.352$)
Oxford	395 (83.7)	77 (16.3)	1.33 (0.96–1.83, $p = 0.084$)	1.73 (1.22–2.44, $p = 0.002$)
Clinical setting				
AMU/IDU	870 (96.7)	30 (3.3)		
Haematology-oncology	320 (87.7)	45 (12.3)	4.08 (2.54–6.64, $p < 0.001$)	3.30 (2.00–5.52, $p < 0.001$)
Presurgical	797 (80.3)	195 (19.7)	7.10 (4.85–10.74, $p < 0.001$)	5.51 (3.71–8.44, $p < 0.001$)

continued

TABLE 4 Regression analysis of location of consented patients (centre-wise, clinical setting-wise and gender) (*continued*)

Dependent: consented				
	Not consented	Consented	OR (univariable)	OR (multivariable)
Age range (years)				
< 30	89 (84.8)	16 (15.2)		
30–39	125 (82.8)	26 (17.2)	1.16 (0.59–2.32, $p = 0.674$)	1.06 (0.53–2.17, $p = 0.872$)
40–49	217 (84.8)	39 (15.2)	1.00 (0.54–1.93, $p = 0.999$)	0.97 (0.51–1.92, $p = 0.938$)
50–59	291 (83.1)	59 (16.9)	1.13 (0.63–2.12, $p = 0.695$)	1.10 (0.60–2.12, $p = 0.756$)
60–69	347 (85.7)	58 (14.3)	0.93 (0.52–1.74, $p = 0.812$)	0.96 (0.52–1.83, $p = 0.891$)
70–79	442 (87.9)	61 (12.1)	0.77 (0.43–1.43, $p = 0.384$)	0.93 (0.51–1.77, $p = 0.806$)
≥ 80	476 (97.7)	11 (2.3)	0.13 (0.06–0.28, $p < 0.001$)	0.23 (0.10–0.53, $p = 0.001$)
Gender				
Female	1269 (89.2)	154 (10.8)		
Male	718 (86.1)	116 (13.9)	1.33 (1.03–1.72, $p = 0.030$)	1.36 (1.04–1.79, $p = 0.026$)

TABLE 5 Regression analysis of 'approached to consented' patients

Dependent: consented				
	Not consented, *n* (%)	Consented, *n* (%)	OR (univariable)	OR (multivariable)
Hospital				
Birmingham	154 (60.2)	102 (39.8)		
Oxford	105 (57.7)	77 (42.3)	1.11 (0.75–1.63, $p = 0.605$)	1.09 (0.72–1.65, $p = 0.685$)
Leeds	114 (55.6)	91 (44.4)	1.21 (0.83–1.75, $p = 0.326$)	1.13 (0.76–1.69, $p = 0.550$)
Clinical setting				
AMU/IDU	37 (55.2)	30 (44.8)		
Presurgical	265 (57.6)	195 (42.4)	0.91 (0.54–1.53, $p = 0.712$)	0.80 (0.46–1.40, $p = 0.433$)
Haematology-oncology	71 (61.2)	45 (38.8)	0.78 (0.42–1.44, $p = 0.428$)	0.69 (0.35–1.34, $p = 0.276$)
Age range (years)				
< 30	21 (56.8)	16 (43.2)		
30–39	35 (57.4)	26 (42.6)	0.98 (0.43–2.24, $p = 0.952$)	1.03 (0.44–2.38, $p = 0.953$)
40–49	53 (57.6)	39 (42.4)	0.97 (0.45–2.11, $p = 0.929$)	1.03 (0.47–2.27, $p = 0.941$)
50–59	67 (53.2)	59 (46.8)	1.16 (0.55–2.45, $p = 0.701$)	1.21 (0.58–2.60, $p = 0.612$)
60–69	79 (57.7)	58 (42.3)	0.96 (0.46–2.03, $p = 0.921$)	0.98 (0.47–2.09, $p = 0.956$)
70–79	76 (55.5)	61 (44.5)	1.05 (0.51–2.22, $p = 0.889$)	1.02 (0.49–2.18, $p = 0.949$)
≥ 80	42 (79.2)	11 (20.8)	0.34 (0.13–0.86, $p = 0.024$)	0.31 (0.12–0.79, $p = 0.016$)
Gender				
Male	122 (51.3)	116 (48.7)		
Female	251 (62.0)	154 (38.0)	0.65 (0.47–0.89, $p = 0.008$)	0.61 (0.44–0.86, $p = 0.004$)

TABLE 6 Demographics of low-risk patients

	ALL			AMU/IDU			Presurgical			Haematology-oncology		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	60	52	43	6	13	2	34	32	38	20	7	3
Age years [median (IQR)]	62.00 (49.00–71.50)	54.50 (41.50–68.25)	60.00 (47.50–73.00)	61.50 (59.50–72.50)	53.00 (39.00–62.00)	67.00 (61.00–73.00)	61.00 (51.75–72.50)	51.00 (40.00–65.50)	58.50 (47.25–72.75)	63.00 (40.00–69.50)	66.00 (56.00–74.00)	63.00 (52.50–68.00)
Gender												
M (%)	27 (45)	21 (40)	21 (49)	3 (50)	5 (39)	1 (50)	10 (29)	12 (38)	17 (45)	14 (70)	4 (57)	3 (100)
F (%)	33 (55)	31 (60)	22 (51)	3 (50)	8 (61)	1 (50)	24 (71)	20 (62)	21 (55)	6 (30)	3 (43)	0 (0)
Ethnicity												
White (%)	35 (58)	42 (81)	38 (84)	3 (50)	12 (92)	2 (100)	22 (65)	24 (75)	33 (87)	6 (86)	12 (92)	3 (100)
Non-white (%)	5 (8)	10 (19)	2 (5)	1 (17)	1 (8)	0 (0)	4 (12)	8 (25)	2 (5)	1 (14)	1 (8)	0 (0)
Not recorded (%)	20 (33)	0 (0)	3 (7)	2 (33)	0 (0)	0 (0)	8 (24)	0 (0)	3 (8)	0 (0)	0 (0)	0 (0)

IQR, interquartile range.

Note

As a guide, not as a formal hypothesis test, there is little evidence of an association between age and (hospital, setting) since a Kruskal–Wallis test yields $p = 0.50$ and a chi-squared test for gender by (hospital, setting) yields $p = 0.10$. Testing for ethnicity might be misleading due to small counts, especially multiple zeroes. Reproduced with permission from Krishna *et al.*[47] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The table includes minor formatting changes to the original text.

TABLE 7 Demographics of high-risk patients

	ALL			AMU/IDU			Presurgical			Haematology-oncology		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	33	25	46	4	4	1	19	19	43	10	2	2
Age years [median (IQR)]	58.00 (53.50–68.00)	60.50 (48.00–64.50)	60.00 (48.75–69.75)	71.50 (64.25–75.75)	58.50 (40.25–72.50)	55.00	58.00 (53.00–64.00)	60.00 (48.50–63.00)	61.00 (48.00–71.00)	57.00 (54.00–61.75)	61.50	63.00
Gender												
M (%)	8 (24)	11 (44)	20 (44)	1 (25)	2 (50)	0 (0)	4 (21)	8 (42)	19 (44)	3 (30)	1 (50)	1 (50)
F (%)	25 (76)	14 (56)	26 (56)	3 (75)	2 (50)	1 (100)	15 (79)	11 (58)	24 (56)	7 (70)	1 (50)	1 (50)
Ethnicity												
White (%)	22 (67)	19 (76)	40 (87)	4 (100)	4 (100)	0 (0)	13 (68)	14 (74)	38 (88)	5 (50)	1 (50)	2 (100)
Non-white (%)	3 (9)	6 (24)	3 (7)	0 (0)	0 (0)	0 (0)	1 (5)	5 (26)	3 (7)	2 (20)	1 (50)	0 (0)
Not recorded (%)	8 (24)	0 (0)	3 (7)	0 (0)	0 (0)	1 (100)	5 (26)	0 (0)	2 (5)	3 (30)	0 (0)	0 (0)

IQR, interquartile range.

Note

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TABLE 8 Direct oral penicillin challenge summary

	ALL			AMU/IDU			Presurgical			Haematology-oncology		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
Undergone DPC (*n*)	47	47	32	4	12	2	29	30	27	14	5	3
Opportunistic de-labelling	44	43	32	1	10	2	29	30	27	14	3	3
Therapeutic de-labelling	3	4	0	3	2	0	0	0	0	0	2	0
De-labelled [*n* = (%)]	45	46	31									
De-labelling rate	95.7%	97.9%	96.9%									

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TABLE 9 Summary of AEs

	Total, *N*	Immediate HSR	Non-immediate HSR[a]	Non-specific[b]	De-labelled *N* =
Oxford, *N*	9[c]	0	1	8	8
Leeds, *N*	2	0	0	2	1[d]
Birmingham, *N*	16[c]	0	2	13	14
Total	27	0	3	23	23

a Mild cutaneous.
b Mild.
c One patient SAE – unlikely to be related to DPC.
d Not de-labelled as patient developed gastrointestinal tract side effects and did not complete 3-day DPC protocol. Reproduced with permission from Krishna *et al.*[47] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) license. See: https://creativecommons.org/licenses/by-nc-nd/4.0/. The table includes minor formatting changes to the original text.

TABLE 10 Detailed summary of AEs

Study site	Participant number	Description	Comment (related/unrelated to DPC)
University Hospitals Birmingham	UH1007	-Diarrhoea and itching (no rash). Headache since admission and during prolonged DPC. Resolving on day 5 follow-up.	• Unrelated to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1010	The patient tolerated the first dose of amoxicillin challenge followed by two doses. Then developed the following: *-Temperature 35.7* *-Haemodynamically stable (HR 97, BP 136/97, SATS 95% on air)* *-Inflammatory markers – raised, diagnosed with 'infection of unknown origin' with deterioration of pre-existing renal function detected by the clinical team (reviewed by renal consultant); creatinine raised and eGFR dropped from 17 to 12. No peripheral blood eosinophilia.* *The clinical team commenced piperacillin/tazobactam to treat the infection (oral amoxicillin was withdrawn).* -There was no evidence for type-I and type-IV HSR. -Above details were reviewed by SPACE investigators, sponsor research and development and oversight committee Chair's and it was agreed that SAE was 'unlikely to be related to DPC'.	• Classed as SAE but 'Unrelated to DPC' • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1048	-Diarrhoea for 24 hours, self-remitting. -Vaginal spotting for 72 hours (urine pregnancy test was negative prior to DPC).	• 'Unrelated to DPC' • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1038	-'Waxy bitter taste' in mouth after taking each dose of PO amoxicillin.	• Likely related to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1047	-Abdominal discomfort after each dose of 'opportunistic de-labelling' (1). -Headache (became milder during the course of DPC) (2) -Non-itchy rash (elbow and dorsum of both hands), mild, appeared on day 2 of DPC and did not worsen despite further doses of amoxicillin, and did not require specific treatment. Photos of rash showed small papular eruptions on elbow flexure and dorsum of both hands (3).	• Likely related to prolonged DPC Side effect of amoxicillin (1) • Unrelated to DPC (2) • 'Likely related' to prolonged DPC (3) • **Not de-labelled**. Referred to allergy services for further investigation

continued

TABLE 10 Detailed summary of AEs (*continued*)

Study site	Participant number	Description	Comment (related/unrelated to DPC)
University Hospitals Birmingham	UH1013	-Mild cutaneous HSR (immediate or non-immediate; time of onset uncertain) or spontaneous urticaria.	• Likely related to DPC • Not de-labelled • Referred to allergy services for further investigation
University Hospitals Birmingham	UH1061	-Felt 'spaced out' (lightheaded) after the first dose of DPC, no other symptoms, vital parameters satisfactory, recovered in 3–4 hours without intervention. Completed course of opportunistic de-labelling.	• Unrelated to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1051	-Localised rash which was not in keeping with immediate or non-immediate HSR to amoxicillin.	• Unrelated to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1069	-Patient-reported 'funny tummy', tensed tummy for approximately 24 hours. Resolved. Completed opportunistic de-labelling with no symptoms suggestive of immediate or delayed HSR.	• Unrelated to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1070	-Headache (known to have headaches), responsive to paracetamol.	• Unrelated to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1074	-Headache -Knee pain (known OA)	• 'Unlikely' related to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1073	-Upset tummy and one episode of diarrhoea on day 4 which the patient related to food, as her husband had similar symptoms. -Non-specific 'rash' on the cheek.	• 'Unlikely' related to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1078	-Headache after DPC first dose, responded to paracetamol.	• 'Possible' related to DPC but not a HSR • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1088	-Previous history of migraines. Reported 'migraine' on day 2 after DPC, settled with paracetamol.	• 'Unlikely' to be related to DPC • No evidence of type-I or type-IV HSR • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1089	-Flushed cheeks with each dose of prolonged DPC ('opportunistic de-labelling) but completed the course of prolonged DPC. -No other signs suggestive of type-I or type-IV hypersensitivity	• 'Unlikely' to be related to DPC • De-labelled for penicillin allergy status
University Hospitals Birmingham	UH1104	-'Itch' occurred within an hour of DPC. This was localised to an area of eczema on the right hand (that had appeared a day prior to DPC). No significant findings on examination, observations satisfactory. Itch lasted until the following morning. Patient completed 'opportunistic de-labelling' as per day 5 follow-up (no rash or concerns).	• 'Unlikely' to be related to DPC • De-labelled for penicillin allergy status

TABLE 10 Detailed summary of AEs (*continued*)

Study site	Participant number	Description	Comment (related/unrelated to DPC)
Oxford University Hospital NHS Foundation Trust	OX3023	-Patient with relapsed multiple myeloma admitted due to hypercalcaemia and renal impairment. -Patient clinically improved, observations were back to normal and renal function steadily improved. Clinical team were happy for patient to be recruited for SPACE study. -Patient stratified as 'low risk' and consented to undergo 'therapeutic de-labelling'. After discussion with clinical team IV co-amoxiclav 1.2 g, twice a day (adjusted as per renal function) was prescribed. -Patient tolerated co-amoxiclav on day 1 and continued to improve then on day 3 started to feel shortness of breath and on day 4 renal function declined. -Chest X-ray showed consolidation and signs of chest infection. -Antibiotic was switched by the clinical team to Tazocin to cover chest infection. -Renal function continued to deteriorate. -Reviewed by respiratory, renal and haematology teams who thought the deterioration was most likely due to the disease progression and chest infection. Free light chain ratio came back 11 days post admission, and it increased significantly, indicated progression of multiple myeloma. -No evidence of type-I and type-IV HSR. -There was protocol deviation with respect to first dose administered IV rather than oral as per study protocol. Sponsor informed. Re-training of study pharmacists was completed. -Above details were reviewed by SPACE investigators, oversight committee Chairs and OUH QA/Governance and agreed that this SAE was 'unlikely to be related' to DPC.	• SAE 'unlikely to be related to DPC' • De-labelled for penicillin allergy status
Oxford University Hospital NHS Foundation Trust	OX3022	-Mild nausea lasting for 1 hour after the dose. Patient could tolerate, happy to take penicillin in the future.	• Likely related to DPC • De-labelled for penicillin allergy status
Oxford University Hospital NHS Foundation Trust	OX3032	-Felt nausea, wanting to vomit and stomach pain. A bit of tingling in tongue but no swelling or worsening. Mild itchiness but no rash or swelling of any part of body. -No type-I HSR.	• Probably related to DPC • Discussed with PI, type-1 hypersensitivity ruled out • De-labelled of penicillin allergy • Side effects of amoxicillin • Updated record to state side effect Patient counselled and happy
Oxford University Hospital NHS Foundation Trust	OX3033	-Nausea a few hours after dose and disappeared a few hours later. -Patient could tolerate and happy to take penicillin in the future.	• Likely related to DPC • De-labelled of penicillin allergy status
Oxford University Hospital NHS Foundation Trust	OX3047	-Stomach cramps, nausea, diarrhoea.	• Likely related to DPC • Possible common and self-limiting side effects of amoxicillin • De-labelled of penicillin allergy status

continued

TABLE 10 Detailed summary of AEs (*continued*)

Study site	Participant number	Description	Comment (related/unrelated to DPC)
Oxford University Hospital NHS Foundation Trust	OX3052	-Fever, muscle ache, sore throat.	• Unrelated to DPC • Discussed with PI, considering the timing of onset and clinical symptoms – indicative of viral infection • No signs and symptoms of type-1 HSR • De-labelled of penicillin allergy status
Oxford University Hospital NHS Foundation Trust	OX3067	-Isolated rash on upper chest, arms and legs appearing on day 2 after an otherwise uneventful supervised DPC in clinic.	• Likely related to DPC • Discussed with PI, consistent with description of previous index reaction and therefore likely cutaneous non-IgE-mediated delayed HSR • Photo sent by patient uploaded in the medical notes • **Not de-labelled**. Prolonged DPC stopped. Allergic to penicillin
Oxford University Hospital NHS Foundation Trust	OX3071	-Tummy ache, like irritable bowel syndrome symptoms (PMH: irritable bowel syndrome following chemotherapy), headache.	• Likely related to DPC • Possible common and self-limiting side effects of amoxicillin • De-labelled penicillin allergy status
Oxford University Hospital NHS Foundation Trust	OX3073	-Tummy ache and diarrhoea	• Likely related to DPC • Possible common and self-limiting side effects of amoxicillin • De-labelled penicillin allergy status
Leeds Teaching Hospitals NHS Trust	4–660	-Started with a bad stomach and feeling generally unwell on the second day following initial DPC so did not take the prolonged course. Patient decided to stop penicillin and took Imodium.	• Classed as AE, likely related to DPC as this was consistent with her previous history of her reported symptoms • **Not de-labelled** • Patient not considered de-labelled for the purposes of the study as course of penicillin not completed
Leeds Teaching Hospitals NHS Trust	4–566	-Patient reported she had a facial cheek redness on Friday (day 3) which had gone by Saturday morning with no other symptoms. History reviewed by local investigator and another member of the steering committee. All were in agreement that this event does not constitute a significant reaction to the DPC and can therefore be considered as de-labelled.	• Classed as AE • DPC recorded as completed • De-labelled

Discussion

This is the first multicentre prospective study from the UK to investigate the feasibility of delivering a DPC by non-allergy specialist HCPs in secondary care. DPC was tested in acute and elective clinical settings including AMU/IDU and haematology-oncology and presurgical units, respectively. A relatively large number of patients with a PAL were screened, and a small proportion progressed to the next stage involving informed consent. The conversion rate from screening to informed consent was very low in an acute setting and significantly higher in elective settings. Amongst those patients who progressed to informed consent, 60% were stratified as 'low risk' across all participating sites, and a very high proportion (81%) of this cohort agreed to undergo DPC. We de-labelled 97% of patients via DPC, this was safe and there were no cases of serious type-I and type-IV HSRs.

This study provided proof of concept data in favour of a non-allergy specialist-led DPC service in both inpatient and outpatient settings, although sample size for the former was very small. We showed that DPC could be safely delivered using a standard operating protocol by clinical pharmacists and nurses supervised by a non-allergy specialist senior clinician at consultant grade. A pre-study workshop enabled standardisation of procedures including patient selection, informed consent, risk stratification, DPC, clinical environment, governance framework, day-5 follow-up, updating PAL status in clinical records and written communication to primary care physicians.

Amongst consented patients, 60% were deemed 'low risk' and this is in keeping with previous studies that reported a broad range of 40–82% for 'low risk' category amongst those considered for penicillin allergy de-labelling.[7,48–50] Majority of 'low risk' patients in our cohort were characterised as 'indeterminate' (50%; non-life threatening and did not require hospitalisation), had a remote history (> 10 years without features of an IgE-mediated reaction; 62% cases), reported mild benign rash (56%) and/or tolerated co-amoxiclav or amoxicillin since the PAL was acquired. Due to lack of clarity regarding the temporal association of the reaction with administration of penicillin and/or other details surrounding the index reaction, a prolonged challenge protocol was employed to exclude type-I and type-IV HSR. We employed amoxicillin for DPC as this is the most commonly prescribed penicillin in the UK, is a representative member of the beta-lactam (penicillin) family and is sufficient to elicit side chain reactivity. Furthermore, this intervention was administered to patients categorised as 'low risk', that is those highly unlikely to have experienced an immune-mediated index reaction. There are no validated challenge test protocols to investigate type-I and type-IV HSRs at present.[51] Some studies employed a single oral dose of penicillin (penicillin or amoxicillin 250 or 500 mg) to exclude both type-I and type-IV HSRs, while others used a single dose followed by 250–500 mg amoxicillin twice daily for 3–5 days.[51] We opted to administer a single dose of 500 mg amoxicillin to exclude type-I HSR followed by 250 mg twice daily for 3 days to exclude type-IV HSR based on our previous experience in specialist NHS allergy clinics and from an AMS viewpoint.

We de-labelled 122 out of 126 (97%) 'low risk' patients with PALs in this study; 3 reported a mild delayed onset rash and 1 patient could not complete the 3-day protocol due to gastrointestinal side-effects of amoxicillin, although type-I HSR was excluded in all the patients. Our data are concordant with previous reports from other countries.[9,34] A systematic review involving a pooled analysis of 13 studies relating to DPCs in 1202 'low risk' inpatients and outpatients reported that 96.5% of cases were de-labelled.[34] There were no cases of serious type-I or type-IV HSRs reported. Forty-one out of 1202 (3.4%) developed mild type-I or type-IV HSRs. In a meta-analysis of 23 published studies (2001–17) involving 5056 PALs, 97% and 86% were successfully de-labelled by DPC and skin tests *and* penicillin challenge respectively ($p < 0.001$); the higher rate in the former group was attributed to a greater likelihood of participants with 'low risk' status.[9] Interestingly, success rates of penicillin challenges were higher in an inpatient as opposed to outpatient settings (97% vs. 86%; $p < 0.001$) and no significant differences were seen in those with and without concurrent bacterial infection during the challenge procedure (with vs. without, 94% vs. 95%; $p = 0.11$).

This study was conducted at three busy secondary care teaching hospitals across England over a wide geographical area. Our screened sample included 11.6% patients of non-white ethnicity (the UK population comprises 18% non-white ethnicity as per the 2021 census) with a PAL. It is plausible that some patients from this group were not considered due to suboptimal English language proficiency, as it was not within the scope of the study to provide patient information sheets in native languages and access translation services. There were 11.4% patients of non-white ethnicity amongst those consented to participate in the study.

Our data suggest that DPCs can be implemented by non-allergy specialist HCPs in the NHS provided relevant personnel are trained, there is a standard operating protocol, and prescribing practices and procedures are standardised and aligned to local governance framework. Specifically, a multidisciplinary team with strong leadership including an allergy specialist and key stakeholders (e.g. trust medicines safety team with clinical pharmacist, microbiologist, ID physician, IT representative, etc.) is needed alongside provision of standardised audit tools to measure performance.

An important observation made in this study relates to low conversion rate and elucidation of reasons for failed progression from screening to informed consent stage of the study pathway. Overall, conversion rate across all sites and all clinical settings was modest at 12%. This was very low (3.8%) in acute settings and significantly higher [haematology-oncology (12.3%; OR −3.30; $p < 0.001$) and presurgical (19.7%; OR −5.51; $p < 0.001$)] in elective settings. The OR for progression from screening to consent stage was significantly higher at Oxford (OR −1.73; $p = 0.002$). The reasons

underpinning centre-wise differences are not entirely clear and were explored as a part of qualitative analysis in WS2 (see *Chapter 3*). Differences in patient demographics, case complexity and local service framework between centres may have contributed. Specifically, AMUs were spread across multiple wards at Leeds during the pandemic creating additional layers of complexity for research staff to contact clinical teams and patients. Screening was led by senior clinical pharmacists (also independent non-medical prescribers) at Oxford and Birmingham as opposed to RNs at Leeds. On further exploration, it was evident that pharmacists and nurses participating in the study had had varying degrees of prior exposure to drug allergy, including time spent in allergy clinics. Irrespective of professional background, it is also plausible that differences in previous knowledge of allergy, including familiarity with obtaining and interpreting a drug allergy history, as outlined, may also have contributed to differences in conversion rates between centres.

In the CATALYST study[49] led by pharmacists involving inpatients in surgical and medical wards in Northumbria Healthcare NHS Foundation Trust, 172 (57%) patients with PAL were excluded similar to the study, although a full breakdown of details was not reported by the authors. In contrast, another single centre non-allergy specialist-led study from Scotland involving 112 inpatients from respiratory and medical admissions units reported a very high conversion rate (92%); 4 patients were excluded due to clinical instability, 3 declined to participate and 2 for unknown reasons.[50] In a dual cancer centre prospective study[48] from Victoria, Australia, 1225 patients with PALs were risk stratified (558 'low risk' and 667 'high risk'). Two hundred and eight of 558 (37%; i.e. conversion rate 67%) 'low risk' patients were not consented to participate due to the following reasons: declined (29.8%), clinician's refusal (5.3%), unwell (18.3%), antihistamine/high dose steroids (8.2%), discharged (34.6%) and 'others' (3.8%). In another single-centre pharmacist-led inpatient study[52] from Australia, 203 out of 309 (66%; conversion rate 34%) patients with a PAL were excluded due to clinical and logistic reasons, such as patient not available at the time of ward round (30%), cognitive impairment (18%), admission in intensive care unit (ICU)/spinal/paediatric unit (11%), palliated status (2%), etc. In a study involving COVID-19-positive patients in a medical ICU in Nashville, TN, USA, only 24 were deemed suitable for DPC out of 2670 (conversion rate – 0.9%) patients with PALs.[53] All 24 cases, however, were successfully de-labelled, although 2 patients developed a mild rash when penicillin was prescribed at a later date. Reasons for unsuitability included haemodynamic instability, mechanical or non-invasive ventilation and inability to give clinical history. Another study from the same centre involving non-COVID-19 patients in medical ICU reported that 240 out of 839 were deemed suitable (28.6%).[54] Reasons for exclusion were the same as in the previous study. Two hundred and five out of 240 (85%) patients agreed to undergo DPC, and 203 patients were de-labelled; 2 (0.9%) developed a non-immediate rash and could not be de-labelled. An inpatient single-centre pharmacist-led study from Auckland reported a very high conversion rate of 96% in a cohort of 250 patients with a PAL.[55] Twenty-four patients were excluded due to mental health issues, cognitive impairment, language barrier, and declining to participate. These studies had similar entry criteria but showed large variations in conversion rates that are difficult to explain. It is possible that the denominator (all patients with a PAL) was not accurately identified in some studies. In addition, patient demographics, case complexity including comorbidities, views, perspectives and behavioural factors amongst HCPs and patients and research governance framework may have contributed to the differences in conversion rates seen in these studies.

One specific difference between the SPACE study and those cited above is that we used a two-step approach in the study pathway. Patients with a PAL were identified and screened as per their Trust electronic medical records and those not meeting study criteria, specifically those who were clinically unstable, and with comorbidities such as severe asthma, severe COPD, significant cardiac problems and factors relating to capacity to consent were not considered. It is plausible this modus operandi may have at least in part contributed to low conversion rates, as other studies approached their participants directly to risk stratify and may have had greater opportunities to accurately assess patients clinically, as per their current status and gain their interest in participation. Interviews with 'low risk' patients in the SPACE study who declined DPC suggested that these were mainly related to their personal circumstances (discussed in *Chapter 3*). The interviews however involved a limited number of patients, so it is plausible that some participants who declined DPC may have had other reasons. This might be worth exploring in future work, so appropriate strategies could be shaped to enhance greater patient engagement with the intervention.

Among the 1055 patients deemed potentially suitable for screening, 412 (39%) were not approached. This was due to logistical reasons such as patients being discharged or relocated to another clinical area, inability to contact over telephone or research team not being able to contact patients in a timely manner due to time constraints.

Sixteen per cent of 1203 ineligible patients did not meet study criteria due to pregnancy, breastfeeding, concomitant COVID-19 infection and/or not having a definitive PAL in their records upon further scrutiny. Some of these patients may have been suitable for risk stratification at a later time point in 'real world' clinical practice. Twenty-two and 28% of cases could not be considered due to lack of capacity to give informed consent and underlying psychiatric/psychological illness respectively but may be considered in 'real world' clinical practice akin to other medical and surgical interventions under appropriate governance framework including support from professional translators with an aim to achieve equity and equality of care and in the interest of the global campaign against AMR. Thirty-six per cent of cases with a PAL were deemed clinically unstable as per study criteria and could not be considered for participation. However, there were cases found across the three participating sites where patients were deemed medically unsuitable at the point of consideration due to genuine medical reasons (e.g. confusion, delirium, uncontrolled blood pressure, cardiac arrhythmia, asthma/COPD exacerbation, heart failure, gastrointestinal bleed, ethanol toxicity, suspected problem with gastrointestinal absorption, frailty, etc.) but may have been suitable at a later time point in a 'real world' clinical practice if there is a mechanism for follow-up to determine an optimal time point to revisit suitability for risk stratification.

Our data showed that an elective setting may be more appropriate to offer DPC ('opportunistic de-labelling') in the NHS. However, with an appropriate service framework in place, it is feasible to deliver 'therapeutic de-labelling' for selected clinically stable 'low risk' patients with an aim to offer penicillin as the first-choice antibiotic, reduce LOS and reduce risk of AMR and other serious hospital-acquired infections. This intervention will also improve national AMS practices, posing a further argument for penicillin allergy de-labelling to be routinely considered in these strategies going forward. Chua *et al.*[48] reported a 10.5-fold increase in the use of narrow spectrum antibiotics amongst de-labelled patients, and a 2-fold increase in improvement in antibiotic prescribing and a reduction in restricted antibiotic usage, all in line with WHO AWaRe framework (https://www.who.int/publications/i/item/2021-aware-classification; accessed 1 May 2023).

Our observations suggest a multipronged approach is needed in routine clinical setting to maximise uptake of DPC. This includes but is not limited to contacting patients at an appropriate and optimal time point time after their clinical condition has improved and stabilised, special approaches including culturally tailored supportive measures for those from ethnic minority groups with suboptimal English language proficiency and an appropriate governance framework for those unable to give informed consent. These approaches would facilitate our efforts to make the intervention more equitable.

This study has limitations. First, the sample size for DPC was moderate at 126. However, this was a feasibility study, and its primary aim was not to investigate safety. Second, very few patients underwent DPC in an acute clinical setting. The SPACE team reviewed conversion rates 3–4 months after commencement of recruitment, recognised the very low conversion rate in an acute setting, and focused efforts on elective settings for the remaining study period in the interest of achieving the target of 122 DPCs in a timely manner, and noted a gradual and steady improvement in conversion rate. While there are data from the USA, Australia and New Zealand (and some evidence from the UK[49,50,52]) regarding the feasibility and safety of DPC undertaken in busy inpatient settings,[17,25,48,53,54] further data are needed from the UK due to differences in service and governance framework. Third, it was not within the scope of this study to investigate the impact of de-labelling on AMS, conduct long-term follow-up and confirm whether patient records were updated in primary care records following formal written communication to patients' GP.

In conclusion, this study demonstrated the feasibility of delivering a DPC to 'low risk' patients with a PAL by non-allergy specialist HCPs in a controlled clinical environment and in a regulated practice framework in secondary care with support and remote supervision of allergy specialists when needed. The uptake of DPC amongst consented 'low risk' patients was very high and 97% of patients who underwent DPC were successfully de-labelled. In the UK NHS, an 'opportunistic de-labelling' service employing DPC in an outpatient setting may offer greater opportunities and an inpatient de-labelling service may be better suited as a specific strategy for 'therapeutic de-labelling' for concurrent bacterial infections in selected patients.

Chapter 3 A qualitative study to investigate individual and organisational factors that may influence penicillin allergy de-labelling

BOX 3 Key messages

- Most patients we interviewed accepted the penicillin allergy record, as they had either been advised by a HCP or they could not recall the event that had led to the allergy.
- Patients stratified as low risk of having a true allergy were keen to have the record reviewed, to benefit themselves, as well as the wider societal benefits of helping with healthcare research.
- There was little to no knowledge or understanding of the impact of having this allergy record. Many patients did not consider that this may pose a risk to their own treatment, but some patients noted that their allergy led them to take multiple courses of other less effective antibiotics.
- Healthcare professionals perceived potential risks to individuals undergoing the challenge as well as their own professional practice and accountability, manifesting into a more risk-averse approach.
- Infrastructure, such as skilled staff, dedicated space and monitoring, and governance, including policies and clear documentation were considered fundamental requirements for the intervention to become routine and successful.
- Timing of the intervention was an important consideration for patients as well as clinicians.
- As many as 1 in 10 people report an allergy to penicillin; most of these are intolerances rather than allergies.
- The impact of spurious allergy labels is considerable to the individual patient as well as the wider healthcare system – in terms of outcomes, healthcare utilisation, finance as well as the risk of antimicrobial resistance.
- People with penicillin allergy records are generally keen to review and improve the accuracy of their records, provided it is the right context and environment.
- Healthcare professionals reported the complexities of managing penicillin allergy records, compounded by knowledge and awareness (of patients and clinicians), skills (such as eliciting an accurate allergy history), acuity of the patient's presentation, infrastructure to monitor, governance and clinical accountability.
- With appropriate resources, training, facilities, and governance frameworks including escalation or referral pathways to allergy specialists and consideration of local contextual factors, our research demonstrates the feasibility of successfully implementing a penicillin allergy de-labelling intervention by non-allergy specialists.

Research questions

What are the behaviours, attitudes and acceptability of patients, HCPs and managers regarding the use of DPC in low-risk patients?

Aims and objectives

Aim

To identify the individual and organisational factors that may influence implementation and adoption of the penicillin allergy de-labelling intervention.

Objectives

1. To gain the individual practitioner and patient perspectives on DPC.
2. To determine potential enablers and barriers for their willingness to undertake or implement DPC.
3. To establish the contextual factors, processes and infrastructure that may influence the implementation and sustainability of the intervention.

Methodology

In this qualitative study, semistructured patient interviews and stakeholder focus groups were undertaken across study sites to collect data on the experiences of those involved and the behavioural insights and changes that may be required for the penicillin allergy de-labelling intervention to be fully implemented.

This report follows the reporting guidelines of consolidated criteria for reporting qualitative research.[56] Our epistemological approach was informed by pragmatism, in keeping with qualitative research nested within an applied mixed-methods study.[57] In this approach, knowledge does not have an external reality but rather must be located in the experience of individuals, and investigated in ways that generate actionable knowledge.

Participants and sampling strategy

Study participants included patients and relevant HCPs.

Patients

Patients were invited to participate in the qualitative arm of the study at the time of recruitment to WS1. Only patients assessed to be low risk qualified for the qualitative study. Written consent was taken by WS1 research staff at each site. Purposive sampling aimed to recruit an equal number of low-risk patients who completed a DPC or who declined the DPC.

Healthcare professionals and other stakeholders

We purposively sampled relevant staff to include representation from prescribers, pharmacists, nurses, microbiologists, allergy specialists, managers and clinical commissioners for inclusion within each site. Participants were invited by e-mail and poster advertisements from each site's PI. Written consent was taken on the day of participation.

Sample size

For patient participants, we anticipated a total of 10–15 interviews at each site, subject to saturation checking.[58] Through targeted patient recruitment, we aimed for a representative interview sample with respect to gender, age and ethnicity.

For staff participants, we anticipated conducting focus groups comprising 8–10 participants, in keeping with previous recommendations for group size.[59]

Study procedures

Patients

Patient interviews were conducted 8 weeks after consent and began in March 2022 for 1 year. One-to-one semistructured interviews were conducted with patients by telephone using a prespecified interview schedule designed according to the aims and objectives stated above (see *Report Supplementary Material 2*). The interview questions were informed by risk perception theories[60] and developed drawing on relevant literature and the principles of qualitative methodology.[60] The interview procedure involved open questions and was iterated and piloted in consultation with our patient and public partners to ensure face validity.

Healthcare professionals and other stakeholders

Focus groups were conducted in November 2022 (site-A and site-C) and January 2023 (site-B). Focus groups were held in person (two sites) and online via Microsoft Teams (one site) at the preference of study participants. Each focus group lasted between 90 and 120 minutes. The discussions were audio-recorded and additional meeting notes were taken by members of the study team (IW, MM). Two members of the research team (YHJ and IW) facilitated the discussions using a prespecified topic guide to prompt discussion, informed by relevant domains of the Theoretical Domains Framework.[61] A copy of the topic guide and relevant participant materials are available in *Report Supplementary Material 2*. Focus group participants were additionally asked to complete an optional short form providing basic demographic data.

Data collection, processing and analysis

Audio transcripts of patient interviews and staff focus groups were collected on a secure digital voice recorder used solely by the research team for this qualitative study. A professional transcribing service (HighTail, London, UK) was used to convert audio files into raw text. Recorded transcripts and text files were stored securely on trusted NHS network servers.

MAXQDA Plus 2022 (VERBI Software, Berlin) was used to analyse the raw qualitative data. The coded texts were extracted for data analysis. One author (MM, a female RP) coded the initial transcripts and summarised the findings. Cross-validation of coding and analysis was independently performed by two additional authors, an experienced female Doctor of Pharmacy (YJ) and a male Professor of Health Policy and Management (IW) who each reviewed half of the coded transcripts and summaries. The final codebook was agreed by all authors. Thematic analysis of the codebook was subsequently undertaken using both inductive and deductive approaches and was informed by relevant domains of the Theoretical Domains Framework.[61]

The researchers sought to be aware of how our own preconceptions might influence data collection and analysis. We engaged in active reflection at multiple stages of data collection and analysis. This involved examining the ways in which the positionality and preconceptions of the researchers influenced the collection of interviews and focus group data, and how data were interpreted and analysed. Important factors included here are that the two data collectors were trained pharmacists and therefore comfortable in probing patients about allergies. The use of telephone interviewing (explained earlier) meant that we were not able to pick up on the visual cues that face-to-face interviewing enables. The research team took care to enable interviewees and focus group participants to be critical when reflecting on the DPC intervention and did not observe any obvious signs of restraint or lack of candidness in this regard. Similarly, in the data analysis process, we sought to consider all possible interpretations of the data, drawing on our PPIE group in the process. To ensure that critical voices were heard we extended our data collection period in order to include patients that had declined the intervention. To ensure that all possible interpretations of the data were considered, early reports of themes were shared iteratively with the wider team, and at the project PPIE panels.

Intervention description

Additional group interviews were conducted in March 2023, involving researchers and clinical leads responsible for delivering the intervention at each of the three sites. The purpose of these was to elicit a detailed description of how the DPC intervention was delivered in practice in the three participating Trusts. The discussions were designed around the template for intervention description and replication framework.[62] The underlying rationale of the intervention ('Why?') is covered in *Chapter 1*. Therefore, this section focuses on site-specific contextual descriptions of materials used in the intervention ('What?'), roles involved in delivery of the intervention ('Who?'), modes of delivery ('How?'), location and infrastructure of delivery ('Where?').

Full details of the intervention description by site are provided in *Report Supplementary Material 2*. In summary: all sites communicated the study information with the clinical teams involved prior to intervention and sent reminders during the implementation. Acute medical arm patients were recruited onsite by the RPs (site-A and site-C) and nurses (site-B) or by direct referrals. Presurgical and haemato-oncology patients were identified using electronic systems or electronic systems-generated theatre and clinic lists and were informed of the study by telephone. Consultant specialists were involved if patients fell between low and high risk, but this gradually lessened as the researchers and the clinical teams gained more confidence. Dedicated space/rooms or necessary equipment including stock of medicines facilitated the intervention delivery.

Results

We conducted 43 patient interviews (summary of participants shown in *Table 11*) and 3 focus groups involving 28 members of staff. *Figure 3* provides a visualisation of the data.

TABLE 11 Characteristics of patient interview participants

	Site-A	Site-B	Site-C	Total
Number referred	28	20	25	73
Number lost to follow-up	13	8	9	30
Number interviewed	15	12	16	43
Of the participants interviewed				
Number of interviews recorded	11	12	14	37
Mean duration of interview, minutes (SD)	12 (5)	8 (3)	9 (3)	9 (4)
Number of non-recorded interviews with notes available	1	N/A	1	2
Number who agreed DPC	14	11	15	40
Number who declined DPC	1	1	1	3
Mean age, years (SD)	62 (13)	65 (11)	56 (16)	61 (14)
Gender				
Female	8 (53%)	5 (42%)	7 (44%)	20 (47%)
Male	7 (47%)	7 (58%)	9 (56%)	23 (53%)
Ethnicity				
White British	9 (60%)	11 (92%)	13 (81%)	33 (77%)
Pakistani	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Mixed background	1 (7%)	0 (0%)	0 (0%)	1 (2%)
Other	0 (0%)	0 (0%)	3 (19%)	3 (7%)
Not specified	5 (33%)	0 (0%)	0 (0%)	5 (12%)
Speciality				
AMU and IDU	0 (0%)	0 (0%)	3 (19%)	3 (7%)
Haematology-oncology unit	4 (27%)	1 (8%)	4 (25%)	9 (21%)
Presurgical unit	11 (73%)	11 (92%)	9 (56%)	31 (72%)

SD, standard deviation. Reproduced with permission from Jani *et al.*[63] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC 4.0) license. See: https://creativecommons.org/licenses/by-nc/4.0/. The table includes minor additions and formatting changes to the original text.

Patient interviews

From March 2022 to March 2023, a total of 43 patients were interviewed (Site-A: *n* = 15, Site-B: *n* = 12, Site-C: *n* = 16). The data are presented in the following sections covering five overarching themes: allergy knowledge, the impact of allergy, decisions about DPC, advice to others and communication. We report themes across the whole patient interview sample, as no notable site-specific differences were identified from the patient interview findings.

Origins of penicillin allergy labels

A small number of interviewees were unable to identify the origins of their allergy labels. Those who were able to remember receiving their PAL were evenly divided between those who had received the label as children and those in adulthood. None of the patients interviewed reported ever having the opportunity to revisit the allergy label.

Unsurprisingly, the group that first received the label in childhood were more likely to have poor recollection of the circumstances or associated symptoms. Some relied on others – most typically a parent – to inform them of the initial reasons for the label. The majority of this group specified symptoms that referred to a rash or sickness and vomiting. One reported having been recorded as allergic following the death of a relative resulting from anaphylaxis.

FIGURE 3 Visualisation of qualitative data by site.

I was very young because in the, I suppose it was late '40s, early '50s, I had a series of injections. The doctor used to come around the house. I think I had Scarlet Fever or something and it was like I reacted with a rash, so they stopped the penicillin. And I can't remember the full details now but that's the reason why I was listed as with an allergy.

Site-C, Patient code: 3021

It was just through my mother, that just from being a child, you know, she just told me that I was allergic … she just used to say that I came out in a rash when I was a baby.

Site-B, Patient code: 611

Well, actually I'm going back when I was a child really. My dad's brother was involved in a car accident and they gave him a penicillin injection, which he was allergic to and he dropped dead outside the hospital grounds, so even though none of the family had been tested for an allergy to penicillin it's on all of our records actually that we're allergic to it, because of that reason.

Site-A, Patient code: 1074

> *I was 6 years old. This was 34 years ago and since then everyone's been scared to check. You were the first one to actually check.*
>
> *Site-C, Patient code: 3057*

Some of those that had been labelled as allergic in adulthood also struggled to recall the circumstances or rationale. Those that did referred to symptoms, such as sickness, rash and a raised temperature. The majority were advised of their allergy by a clinical practitioner (i.e. GP or dentist), although a small number self-diagnosed.

> *That goes back such a long time. The only thing I can remember is I must have had the reaction because the doctor put a note on the top of my notes that I could not have penicillin again because I had a reaction. I don't know how old I was, and I don't know what I was taking penicillin for.*
>
> *Site-B, Patient code: 566*

> *Years and years ago I went to a dentist for some treatment and he gave me some Amoxycillin and I think within a few hours I was pink and spotty. But that was a very long time ago!*
>
> *Site-C, Patient code: 3043*

> *Well, I cut my hand, and I was having it fixed, and they had to give a tetanus and penicillin injection, and put it in my left leg, fine. I got home and all of a sudden my leg swelled up and I could hardly walk on it. I've had tetanus before, and so it must have been the reaction to the penicillin, so I said I'd never have it again, and I didn't until I went on this course. [The doctor] said it could just be a one-off, it could have been the tetanus, it could have been penicillin, or it could have been where the injection was put in … it was me that said I'm not having it again … I just said I don't want penicillin, that was my decision.*
>
> *Site-A, Patient code: 1056*

For most of the patients within our interview sample, the events that triggered the original PAL did not appear to have engendered high levels of ongoing fear or concern, and this may have contributed to their willingness to participate in the DPC intervention.

Patient knowledge of penicillin allergies

Patient interviewees were asked what they knew about penicillin allergies prior to their participation in the study. In every case, their self-assessment was that they had little or no knowledge, as exemplified in comments such as *'not a great deal'*, *'I never looked into it'*, *'I don't know a lot about it at all'*. On further probing, it became clear that there was in fact some variation in knowledge levels, with individual patients referring to, for example: the high prevalence of PAL; common symptoms of allergic or adverse reactions; the origins of penicillin as a treatment and impacts on the treatment options available to them. In most cases, this knowledge stemmed from clinical encounters and, in a smaller number of cases, from the experiences of family members. A consistent message was that patients were inclined to accept the label as valid and therefore not to seek out any more information. None reported awareness of the potential for de-labelling.

> *I was told I was allergic to it and that was it, I just kept well away from it, so I didn't do any further research because, you know, oh well if I was told I can't have it then it was sort of not worth looking at.*
>
> *Site-C, Patient code: 3029*

> *I mean my brother was diagnosed with it and when I spoke to him he said he's definitely got it but I don't know how he came to that conclusion, whether they tested him or not, but my, also my sister says she has an allergy to it. But I don't understand the full, what I know is I had a reaction of a rash but that's all I, that's about all I know really.*
>
> *Site-C, Patient code: 3021*

> *I know that penicillin is supposed to be a better form of an antibiotic than the standard antibiotics, so I've been told.*
>
> *Site-B, Patient code: 622*

> *I always thought, well there's alternatives, and I thought perhaps the alternatives must be as good as penicillin. I mean I shouldn't, I'm an amateur right? I hadn't a clue as regards the effectiveness either of penicillin or their substitute. The substitutes that they gave me always seemed to work actually so it didn't bother me.*
>
> *Site-B, Patient code: 745*

Some patients had reflected on their lack of knowledge in light of the information provided to them during recruitment to the study.

> *Because it's always been on my record, it's not something I've actually looked into if that makes any sense. I always kind of feared it because of the outcome of my uncle. But to be honest I would like my daughter to be checked as well now, because you know, it's silly really to have it on the record if she's not allergic to penicillin.*
>
> *Site-A, Patient code: 1074*

Overall, the patients seemed content to accept the PALs that they had been given and were either unaware or unconcerned by any risks or constraints that these created. However, a large proportion indicated that they had valued the information received during their recruitment to the study, and this knowledge had clearly impacted upon their willingness to consider undertaking the DPC intervention.

Impact of penicillin allergy label

The majority of patients interviewed did not report a direct impact of having a documented PAL. In most cases, this was because alternative treatment options were available and appeared effective. Some noted that it limited the choice for the prescriber.

> *Well every time I've had to have some sort of medicine and they've avoided penicillin it seems to have worked so it hasn't really bothered me at all.*
>
> *Site-C, Patient code: 3038*

> *Well, it's not really affected me per se, but obviously, it cut down the options that were available by clinicians.*
>
> *Site-C, Patient code: 3039*

Some patients reported an awareness of the adverse impact of having a PAL, for example, receiving multiple courses of second-line antibiotics and limited effectiveness of these.

> *…basically they give me some antibiotics but not good as penicillin … probably I will [not] have to go to operation … but they give me five different courses of antibiotics and it doesn't work on my infection …*
>
> *Site-C, Patient code: 3057*

> *I don't think it's really made much difference to be honest with you, other than perhaps maybe when I've had to take antibiotics that penicillin might have cleared things up a bit quicker than the standard things that I've been taking.*
>
> *Site-B, Patient code: 662*

> *… it was difficult to find an antibiotic that may have been appropriate and effective, and they did offer one, it was a new antibiotic but there was consequences to taking it in regards to [Achilles] tendons if you've got any weakness there and unfortunately I did, after many years of sport, so I couldn't take that, so it was a standard antibiotic they used, and I felt that it took longer for the, you know, the pneumonia to dissipate …*
>
> *Site-A, Patient code: 1047*

A few patients reported adverse effects to second-line choices, and others reported a broader impact on their health-related decisions.

> *I used to get prescribed Azithromycin which always made me horribly sick.*
>
> *Site-C, Patient code: 3005*

> *So they had to give me a mixture of other things which with my first child meant that I couldn't breastfeed her so that impacted our lives then.*
>
> *Site-C, Patient code: 3033*

> *I were more concerned with I couldn't take it, … and two separate years I've had a tick bite, and they was really nasty, and I mean once they put me on an antibiotic and I was sick straightaway with that one, really vomiting, and that they didn't really work well.*
>
> *Site-B, Patient code: 828*

Patients' confidence and knowledge about antibiotics affected the impact of their PAL. For example, for some patients it meant they did not consider any impact of second-line alternatives or did not question their doctor's decision to document a PAL in their medical records and for others, it allowed them to request alternatives and be more involved in their own care (shared decision-making).

> *… anyway the medication they give me it cleared it up in two days, but by then she'd already put it on my results I were allergic to it, which you know, at the time I thought, I were a bit suspicious about it, but I can't argue with me doctor like, you know …*
>
> *Site-B, Patient code: 664*

The decision to participate in the direct oral penicillin challenge

As already noted, the majority of patients recruited to the study agreed to undergo the DPC intervention. We sought to understand the reasons behind this decision. Clearly, it is also important to understand why patients might choose to decline the intervention and we therefore sought to include any such patients in our sample of interviewees. At the end of recruitment to this WS, we were able to include three patients in this category.

Reasons for agreeing

While a small number of patients did not cite any reasons for agreeing to the DPC (e.g. 'I've no idea. I just did it'), others cited a range of factors. These can be separated into five categories relating to: patients' knowledge of penicillin allergy, perceived benefits to themselves, clinical advice, altruism opportunism.

An underlying reason for many patients' decisions was the desire to know more about their allergy status. For example, some had not realised that a test to determine the validity of their PAL was possible. Others reported a prior suspicion that they were not actually allergic and so welcomed the opportunity to confirm this. Others had no firm view but were 'curious' or 'interested' to find out if the label was accurate, especially in cases where it had first been given many years before. Others felt that the knowledge provided by the intervention would help to allay fears associated with the PAL. Finally, some interviewees made their decision based on the explanation provided to them by the study team.

> *I've had penicillin or penicillin types, Ampicillin, Cloxacillin, for years. In 1970 when I lost my hand, most of my hand, I were dosed up with it, and I thought my hand were going to go rotten altogether and be no good. So I've had plenty of them, I had big bottles full and I thought well how come all of a sudden I'm allergic to it? So that's what I thought. I always thought no, I'm not.*
>
> *Site-B, Patient code: 467*

> *I was so happy [laughs] when they asked me if you want to be the part of this study. I said I don't mind. Basically, I wanted to get rid of this fear from my head, because I'm so old and I'm regularly getting treatment for my cancer and this and that, and if I needed them my doctors shouldn't be thinking twice before they give me any antibiotics.*
>
> *Site-B, Patient code: 776*

> *When the lady rung me to speak to me about it, like even the first time I spoke to her she was so good explaining it to me, she was brilliant. So I never had any worries or any questions because she was just so good explaining it. It was just, yeah.*
>
> *Site-A, Patient code: 1048*

Other patients recognised the potential benefits to themselves of the removal of their PALs. These included improvements in their treatment through access to penicillin, recognition of the relative ineffectiveness of alternative treatments, and a general sense of making their experiences as a patient more comfortable.

> *um, it just opens my options for the future because if I do get ill again I know that I can take penicillin without any sort of allergic reaction as such so it was, yes, it helps out with studies but it was more along the lines of if I am or if I'm not allergic.*
>
> *Site-C, Patient code: 3047*

> *I've had cancer so I thought it'd be quite good to get de-labelled in case I need any more antibiotics in the future.*
>
> *Site-C, Patient code: 3021*

> *Some of the other things that they've had to give me, I can't remember exactly what it was, but there's times where they've had to give me two or three different things in a combination and they've made me feel really, really ill. So it felt like it would, especially because I've had 39 years without having penicillin, I felt that the risk was worth taking because it would benefit me and I could have penicillin in the future.*
>
> *Site-C, Patient code: 3033*

> *Over the last year or two, when I've been asked and I've said I'm allergic to Amoxycillin, I just thought it would be good to find out, you know, and if I could have it in the future it would be beneficial, so yeah, I was keen to do it.*
>
> *Site-C, Patient code: 3044*

As noted, others were persuaded of the potential benefits when the study was explained to them. This is a potentially significant finding as it indicates the importance of the intervention being accompanied by a verbal rationale and reassurance from a trusted clinician. A smaller number of interviewees still opted to further discuss the proposed intervention, typically with their families, before consenting.

> *The reason I was doing it is because I've ended up with this bone infection, with a severe ear infection but it's the Erythromycin, so it's doing a job but they said penicillin would be much more effective if I could tolerate it.*
>
> *Site-C, Patient code: 3029*

> *Well in the information they gave me they said that when I was being treated, for various allergies or complaints, that the best treatment available was penicillin and that that was far more effective than any other medicines available, and that I was suffering as a result probably that, maybe being satisfied with second best rather than having the best.*
>
> *Site-B, Patient code: 745*

> *Well to be honest with you I'm due to have a gastric bypass operation, and apparently, penicillin is one of the antibiotics that they use, so I think they wanted to check me for that prior to my operation.*
>
> *Site-A, Patient code: 1074*

One of the most cited reasons for consenting was an altruistic motivation to make a contribution to science and, by extension, to future patient care. This response was connected to a willingness to participate in research, suggesting the potential benefits of finding ways to continue to harness altruistic motivations after the study is completed.

> *I've got a few underlying health conditions so to be honest I just thought if it can help someone else I'll do it, you know.*
>
> *Site-C, Patient code: 3022*

> *Well, it's just to help medical science I suppose.*
>
> *Site-C, Patient code: 3036*

> *Well, I think everybody has a duty to the NHS to do the best they can to help with research and all of that kind of thing, and I was in the hospital, I was going to be there for two hours so I said, 'fine, go ahead and do it.*
>
> *Site-A, Patient code: 1044*

It was clear that for many interviewees, their PAL was not a source of significant concern, and their decision was driven mainly by a combination of opportunism and convenience. For these interviewees, the extent to which they would seek out an opportunity for de-labelling was constrained by considerations of expedience.

> *A lady came round and said 'Oh, how long ago were you, do you think that you were allergic to it?' and I said just years and years ago, and then she said 'do you want to do a trial?' and I thought well, while I'm in hospital, I was in the hospital for five days, I just thought well, I'm getting monitored here 24 hours a day, that would be the best time to give it a go, so I just went ahead with it.*
>
> *Site-C, Patient code: 3038*

> *I was happy to go ahead while I was under such heavy supervision.*
>
> *Site-C, Patient code: 3039*

> *I just thought well [laughs] whilst I'm going to hospital, in and out, I might as well just go the whole hog and just try and find out whether I am actually allergic to it or not, because I've never actually taken a test before, so I just thought, okay, let's go for it, see what happens.*
>
> *Site-B, Patient code: 662*

These five categories of motivators – relating to knowledge, perceived benefits, clinical advice, altruism and opportunism – were sometimes cited in combinations by interviewees, suggesting the presence of multiple considerations behind their decisions.

> *I just thought it might help future people and it might help me because it's been such a long time and your bodies change and I just thought well, I might be able to have penicillin which will be better for me.*
>
> *Site-B, Patient code: 566*

> *I thought it would obviously help their research because they explained the research quite in depth but also, it's to their benefit but it's to my benefit as well. Obviously, if you're allergic to something it'd be nice to know definitively.*
>
> *Site-A, Patient code: 1051*

Reasons for declining

As noted, three respondents had declined the DPC. In each case, the reasons for this are related to poor health, inconvenience or a combination of both these reasons.

> *I've just been really unwell since July with cancer, and I just didn't want to put myself through anything else.*
>
> *Site-C, Patient code: 3037*

> *I think basically I just got cold feet because I thought, there is so much going on at the moment health-wise that I just didn't want to complicate anything. And I think that's basically the reason why I did ring and say, 'no I don't actually want to do this' … There was some discussion amongst friends and family, and I suppose, not pressure but the overriding feeling was you know, 'why are you going to do this if you know you've got enough that's happening?'*
>
> *Site-A, Patient code: 1035*

> *Part of the issue is that I'd only just found out that I required surgery. I spend a lot of time out of the country and so arranging a practical sort of process would have been difficult.*
>
> *Site-B, Patient code: 794*

These are clearly reasonable and understandable grounds for reluctance to undergo the DPC. However, the circumstances that prompted this reluctance were far from being unique to the three patients who declined. The difference would appear to be that the positive factors outweighed these concerns for other patients in the sample. For example, others vocalised similar concerns but nevertheless opted to undergo the DPC.

I don't really know actually. I mean she caught me when I was in hospital so I probably just said yes, I don't know. And I nearly regretted it if I'm honest because I had such a bad operation and I had so many issues after the operation I nearly bailed because I just didn't want anything else to go wrong but I figured, well I might as well see if I am allergic to it because it does make sense that I have another option of an antibiotic if I need it.

Site-C, Patient code: 3049

The three declining patients all expressed openness to revisiting the intervention at some future point, especially when their illness or treatment regime afforded them more time and capacity. One further suggestion was for additional support at home.

I understand how the trial goes ahead but I think at the back of my mind was the period when you are at home with the penicillin tablets because I think you take them for three or four days, I can't quite remember now, and I perhaps didn't feel that at that point in the study there was enough easily available support if you needed anything. So, that was sort of at the back of the mind but that wasn't the main sort of factor.

Site-C, Patient code: 1035

Concerns about undergoing the direct oral penicillin challenge

Interviewees were asked what if any concerns they had about the DPC. The majority did not experience major doubts and, in many cases, this assurance appeared to stem from the DPC being conducted in a hospital setting as well as from their 'total confidence' in the staff involved.

I had two nurses that sat right there with me while I, while I took it and for the time afterwards whilst two of the immunologists or whatever they are. So yeah I felt like it was quite safe.

Site-C, Patient code: 3033

I would have had concerns if they'd have sent me away outside of hospital because obviously if I did start having a rash or have a severe reaction to it then obviously I'd be, I wouldn't be in healthcare hands.

Site-C, Patient code: 3038

I think if they'd just sent me some penicillin and said, 'try them and see how you get on', then yes I wouldn't have done that but taking them in a hospital, that's fine. I thought, well if anything does happen, I'm in the right place.

Site-A, Patient code: 1051

Some patients who consented nevertheless had concerns, especially immediately before and during the DPC. For some, this was expressed in a simple statement of being 'scared'. Others recalled symptoms associated with their initial label and expressed concern at these being repeated.

Yeah I talked to another lady on the morning of the test, just you know my nerves and, but they assured me that they would give me an antidote or whatever you call them as soon as I showed, if and when I showed any signs of an allergic reaction.

Site-C, Patient code: 3049

Yeah, I did have concerns, but then I just thought well you know, you've just got to help out with research, and, you know, my priority was to give back something … The concerns were in case anything major was to happen, because mum wasn't too sure, because I didn't know what you know, what outcome of the allergies were, and mum could only remember rashes, so yeah, I was a bit concerned of what could happen, but yeah I just wanted to give back something really to help out with research.

Site-B, Patient code: 611

I was a little bit apprehensive, just you know, wondering what might happen, and because it was quite unpleasant when I broke out in a rash last time if that was the cause, obviously I don't know now. But yeah I was a little bit apprehensive about it … I just decided to do it myself, but I spoke to my wife about it, but you know, she says, fine, if you're happy to do it, do it, so I chose to go ahead.

Site-B, Patient code: 662

Experience of direct oral penicillin challenge

All participants reported positive experiences with the DPC, indicating that the process was well managed, with clear communication and advice. Facilitators for participation included reassurance of being observed, ease and simplicity of the DPC, use of oral formulation and travel reimbursement to attend the DPC. No negative experiences or feedback comments were reported.

Advice for direct oral penicillin challenge process

The only feedback about the DPC was to raise awareness about it so that more people could access it and have the label reviewed.

Advice to others to have direct oral penicillin challenge

Nearly all patients suggested that they would recommend others who have a PAL to undergo risk stratification and if low risk, a direct penicillin challenge.

> *I think it depends on how severe it is, and if it's very mild which I presume mine was, then you should take the test, but if you've got problems like you know, life threatening ones, like your tongue is swelling up or something like that, then I don't think you should risk it.*
>
> *Site-A, Patient code: 1077*

They conveyed their own experience and assurance in knowing being more helpful than uncertainty, especially if it meant they could receive the first choice of penicillin antibiotics. Approximately half the participants expressed this view on the basis of the discussion and advice from the study team.

One participant also noted that the option to have the DPC should be based on individual preference and choice.

> *… it is a personal choice, but who'd want to keep a label that you know, was perhaps incorrect at the time, misinterpreted? It wasn't given to me maliciously or anything*
>
> *Site-A, Patient code: 1061*

Communication about their allergy

General practitioner communication

All patients expressed a preference and expectation that the change in their PAL would be communicated to their GP by the study team and therefore updated on their record. This preference was partly because of the challenge of being able to arrange an appointment with their GP.

> *Only because I only got my letter one day this week and I've been away. This was my first day back today, so I haven't had time to ring my GP yet but I will do.*
>
> *Site-A, Patient code: 1048*

> *I'd just let the team get in touch … Because just trying to speak to my GP it's just, it's a nightmare.*
>
> *Site-A, Patient code: 1051*

Some indicated they would confirm their revised allergy status when they next needed antibiotics or when they went to see their GP. A small number indicated that they had already contacted the GP about the change in allergy status.

Future communication about allergy status

Despite the belief and assumption that the outcome of the DPC would be communicated to the GP and updated on their medical records, many patients reported uncertainty about how to respond if asked about their allergy status in future.

> *It was strange to always say I just have an allergy to penicillin but now I've been tested and I don't have an allergy to penicillin. So yeah, I guess I would, I just wouldn't mention it.*
>
> *Site-C, Patient code: 3033*

Some indicated that they would still mention the historical label to make the HCPs aware in case of any reactions or need for close supervision if penicillin antibiotics were prescribed. This would appear to be an important finding and one which suggests the need for engagement across secondary to primary care if the full benefits of the intervention are to be realised.

> *"I think I might say, well I was down as being allergic but I've been de-labelled, you know, through this study. But I did ask the pharmacist before I left the hospital and she seemed to be saying that I could just say I've no allergies, so I'm not really sure what, you know, what to say.*
>
> *Site-C, Patient code: 3044*

One patient expressed that the severity of the condition requiring antibiotic treatment would also influence the information they shared.

> *I think it depends on the circumstances really but I think if it was something you know like, oh I don't know like sepsis or something like that I would explain that I for years was under the impression I was allergic to penicillin but I'm not anymore, you know?*
>
> *Site-A, Patient code: 1044*

Many noted that the way they responded about their allergy status would change over time.

> *Probably as time passes I'll just say no allergies, but on the other hand, I did… somebody asked me the other day, I can't remember where I was, and I said, 'I've just been de-labelled as allergic to penicillin.'*
>
> *Site-A, Patient code: 1061*

Focus groups with healthcare professionals and other staff

A total of 28 participants were involved in the focus groups across the three study sites (*Tables 12* and *13*). Analysis of the findings of the focus groups was informed by the Theoretical Domains Framework[61] to understand the cognitive, affective, social, environmental, organisational and professional influences on behaviours relating to penicillin allergy status de-labelling. Eleven of the 14 domains were identified as likely relevant to the participant's perceptions of the intervention and changing behaviours for future implementations.

Knowledge

The focus groups involved in-depth discussion of the levels and types of knowledge required by patients and staff to carry out the intervention. In particular, knowledge levels among those delivering the intervention were considered. Some participants emphasised the basic training needs of those involved in delivering the intervention.

> *The team are made up of research nurses and research practitioners … from an … allied health professional background with their own set of skills and are not aware of penicillin, have never given penicillin. And so quite early on we identified that there was a training need there. … I think the concept of the study in itself is an important one but … a lot of education and training needs… for it to work in, in practice.*
>
> *Site-B, Research Practitioner*

A range of opinions were voiced in relation to the risk stratification process and how much specialist knowledge is required. For example, a participant in the Site-C group stated:

> *Maybe in a way, people perhaps, you know, in secondary or tertiary care think that everything is so specialist and has to be really complicated and complex, but actually, the risk stratification tool is well laid out, and if you ask a series of questions and the patient says yes or no to them, you have your answer. And … perhaps people think that it's much more complicated than it is, or it will take much more time, but actually it could be actioned by anyone.*
>
> *Site-C, Research Pharmacist*

By contrast, participants in Site-B found the process more complicated than they had anticipated, partly due to limited knowledge of managing allergies.

TABLE 12 Summary of focus group participants roles

	Site-A	Site-B	Site-C	Total
Total number of stakeholders	13	8	7	28
Roles (self-reported by the participants)	1 Commissioner Representative 1 Consultant Acute Medicine 1 Consultant Anaesthetist 1 Consultant Infectious Diseases 1 Consultant Microbiologist 1 Consultant Respiratory Medicine 1 Foundation Trainee Doctor 1 General Practitioner 1 Research Consultant Immunologist 2 Research Pharmacist 1 Specialist Trainee Doctor 1 Staff Nurse	1 Consultant Anaesthetist 1 Consultant Haematologist 1 Consultant Infectious Diseases 1 Research Consultant Anaesthetist 1 Research Nurse 2 Research Practitioner 1 Staff Nurse	1 Administration Manager 1 Consultant Anaesthetist 1 Consultant Pharmacist 1 Research Consultant Immunologist 1 Research Pharmacist 2 Specialist Nurse	1 Administration Manager 1 Commissioner Representative 1 Consultant Acute Medicine 3 Consultant Anaesthetist 1 Consultant Haematologist 2 Consultant Infectious Diseases 1 Consultant Microbiologist 1 Consultant Pharmacist 1 Consultant Respiratory Medicine 1 Foundation Trainee Doctor 1 General Practitioner 1 Research Consultant Anaesthetist 2 Research Consultant Immunologist 1 Research Nurse 3 Research Pharmacist 2 Research Practitioner 2 Specialist Nurse 1 Specialist Trainee Doctor 2 Staff Nurse

TABLE 13 Characteristics of focus group participants

	Site-A (%)	Site-B (%)	Site-C (%)	Total (%)
Gender				
Female	4 (31)	6 (75)	6 (86)	16 (57)
Male	9 (69)	2 (25)	1 (14)	12 (43)
Ethnicity				
Arabic	1 (8)	0 (0)	0 (0)	1 (4)
Asian or Asian British – Indian	4 (31)	0 (0)	1 (14)	5 (18)
Asian or Asian British – Pakistani	2 (15)	1 (13)	0 (0)	3 (11)
White – British	2 (15)	4 (50)	4 (57)	10 (36)
White – Irish	1 (8)	0 (0)	1 (14)	2 (7)
White – Any other white background	0 (0)	0 (0)	1 (14)	1 (4)
Did not state	3 (23)	3 (38)	0 (0)	6 (21)
Age, years				
20–29	1 (8)	0 (0)	0 (0)	1 (4)
30–39	2 (15)	2 (25)	1 (14)	5 (18)
40–49	4 (31)	1 (13)	2 (29)	7 (25)
50–59	2 (15)	2 (25)	2 (29)	6 (21)
≥ 60	1 (8)	0 (0)	2 (29)	3 (11)
Did not state	3 (23)	3 (38)	0 (0)	6 (21)

> *We thought it would be a case of … you just get patients to tick the box. And if … they say yes to this, that and the other, then they're OK to be de-labelled and, you know, anyone can do that … But I think what we've learned is that it's not a tick box job. Patients just don't fit. There's always some aspects of the history that makes it a little bit less certain and you just can't really quite be sure. Maybe if we were doing hundreds and hundreds of patients, people would feel, you know, effectively it's like having allergy training by the time you've done hundreds of them …*
>
> *Site-B, Research Consultant Anaesthetist*

> *It's difficult for people without a background in formal allergy training to be able to risk stratify, I think, confidently.*
>
> *Site-B, Consultant Anaesthetist*

On further probing, one of the main challenges was the shift in emphasis over allergy history taking, from the usual focus during training on how to *avoid* treatments, to how to *reintroduce* treatments in the event of an inaccurate label. This important difference necessitated additional training to build confidence for non-allergy specialists. Participants at site-A also reported similar challenges but felt that these could be overcome with a gradual, practiced approach over time.

> *I think as a non-allergy specialist there's a lot that you need to grasp, the emergency side of things, because as a pharmacist you don't get involved in that. Then learning how to take an allergy history, so, you know, drug histories are very different to taking an allergy history, knowing what to ask and knowing why I needed to ask that. And then over time, I've built up experience. I think I can see clearer now through allergy histories but it's taken me over a year to be in this position.*
>
> *Site-A, Research Pharmacist*

It was clear that some base level of education was also required for those outside of the immediate context of the intervention. For example, a participant at Site-C referred to holding 'a number of General Practitioner days', which included imparting generalised knowledge on the medical harms of PALs as well as specific information on the GP's role in adopting the DPC intervention. This was echoed by participants in Site-A who also linked this raised knowledge to greater 'passion':

> *I think you'd need to set up some teaching sessions essentially to raise awareness, to raise the passion amongst primary care to de-label people essentially.*
>
> *Site-A, General Practitioner*

A key recurring theme was the knowledge gaps caused by poor medical record keeping. Once recorded, the information influenced decisions made by others involved in the medicines management process.

> *I think without sort of a widespread training package across all nurses or at least having sort of set ones that are happy to do it … You have to make sure to spread across the entire ward. You couldn't have the nurses today being happy to give them the penicillin, but the one tomorrow isn't. So therefore, they're not getting established treatment.*
>
> *Site-B, Staff Nurse*

Patient knowledge levels were also identified as an important factor, with the need for education in, for example, the distinction between drug intolerance and allergic symptoms. The focus group participants' perceptions appeared to echo the main themes from patient interviews in this regard, that is it was felt that timely information delivered by the clinical team could overcome many of the concerns and apprehensions. A counterview expressed by one participant was that patients were just as likely (if not more) than clinicians to appreciate the underlying rationale of de-labelling. The knowledge to explain why an allergy label has been documented in the first instance and the need to review in the future were seen as being equally important, with the awareness that some patients may not want to question the doctor, despite being uncertain of being given the allergy label.

> *On a personal level I think it's made me really think and also explain and discuss with patients, and getting across to my colleagues as well that you can probe into the history of their allergies, discuss it with them, and then explain to them the*

> *significance it does have for their treatment … I think a patient often comes in and says I'm allergic to this, and they don't really realise that it has consequences for their medical treatment in significant ways.*
>
> *Site-C, Specialist Nurse*

> *I think patients intuitively understand the problem with being labelled as penicillin allergic. I think they have just as good a grip on that as lots of healthcare professionals.*
>
> *Site-B, Research Consultant Anaesthetist*

A note of caution was sounded in two of the three focus groups about the readiness and health knowledge and literacy of different patient populations for this type of intervention.

> *I think engaging with a study like SPACE definitely involves a degree of health literacy. And I think that generally the people that we see coming in to be de-labelled are quite articulate people and they've got a really good working knowledge of their own health and their problems and all the appointments and things like that and how they interact. It would be quite interesting to know a bit more about the health literacy of people who were not engaging and not wanting to come in because I suspect that this study is probably representative of a lot of studies where certain people in society, find it easier to engage in things like this than others.*
>
> *Site-B, Consultant Anaesthetist*

One suggestion was to involve primary care pharmacists in the process of educating patients with PALs prior to their DPC in secondary care.

> *I was thinking whether it would be an idea for one of the clinical pharmacists to have a group of these patients prior to them going for de-labelling for them to talk to the patients. to speak to them about why it's important to be de-labelled. So a lot of that work could be done before they came to secondary care, so that the understanding was there for the patient.*
>
> *Site-A, General Practitioner*

Overall, these findings suggest that ensuring appropriate knowledge levels across the full range of stakeholders was critical as any 'weak link' in the chain of intervention implementation threatened to undermine its potential benefits overall. For those directly involved in intervention delivery, there was some divergence of opinion as to how much knowledge could be codified into a 'tick box' or checklist approach. This would appear to have significant implications for future adaptation of the DPC intervention, including the amount of time and resources devoted to allergy history taking and the approach to training built into this.

Skills

Ensuring that HCPs were appropriately skilled at taking a complete and comprehensive allergy history was a consistent theme across sites and amongst all the participants. Different professional groups identified different skills that were necessary during the study for the research staff, as well as those that may be necessary in the future. For example, nurses reported that comprehensive drug history taking was something they were less likely to perform in routine practice, whereas from pharmacists this was embedded.

> *Nurses aren't taught how to take … well when I qualified, they were not taught to take allergy histories. You learn from your mentors and if your mentors don't do it, and I can't think I ever saw my mentor do it, then you don't learn it.*
>
> *Site-C, Specialist Nurse*

In terms of future implementation of the intervention, the role of junior/trainee doctors in allergy history taking was also highlighted.

> *… if you see penicillin allergy whatever you do have you asked these questions? Have you made sure that that was a true allergy or just some intolerance or side-effect of medication? So this is something it will take a good few minutes to go through these questions and I think the junior doctors can get the information about it.*
>
> *Site-A, Foundation Trainee Doctor*

> *… medical schools have a list of core subjects, right, so if antibiotic resistance is on the national risk register we have to argue that taking a history in allergies is an important core skill, just as much as prescribing is an important core skill. If we can achieve that as a country then you'd educate the whole mass of doctors, to be able to make, to discriminate between what is a genuine allergy history and what is a spurious history …*
>
> *Site-C, Research Consultant Immunologist*

These knowledge and skill deficits were considered to be most challenging in clinical settings with high volumes or turnover of staff who would otherwise be unlikely to build up sufficient experience in delivering the DPC.

Professional role and identity

The role of each member of the multidisciplinary team at different stages of the patient's journey, as well as their own professional roles and boundaries, were seen as important in influencing confidence and beliefs about their capabilities (see *Beliefs about capabilities*).

> *… this issue of specialist versus non-specialist and it sounds like what you're saying is it's not either or, it's not you know, total lack of involvement from the specialists, what's the fine nuance? What's the right blend of … so you were saying it happens in teams, so you have access to specialist advice if you need it …*
>
> *Site-C, Focus Group Facilitator*

> *Maybe I'm a sceptic but I think everyone's in their silos …*
>
> *Site-C, Consultant Anaesthetist*

Experts and specialists noted that they had a professional role in encouraging and promoting the appropriate assessment and review of allergy labels across all sectors. In view of the challenges of general practice (including limited time appointments and opportunities to monitor), HCPs in secondary care were thought most appropriate to have a greater role in this than primary care colleagues. However, the role of raising awareness and providing training to shift the culture and approach was recognised as a longer-term strategy/option for primary care. A broader societal/moral role was also outlined to promote and practice AMS.

The role of all clinical professionals in eliciting comprehensive information from patients and educating/advising on the implications of incorrect allergy labels was also highlighted.

Beliefs about capabilities

Respondents commented on the beliefs about their own and others' capabilities in being able to apply the intervention. The combination of knowledge, skills, professional role, clinical expertise and level of experience contributed to the level of confidence they exhibited and expressed.

> *… And there's no foundation doctor who's ever going to think, 'oh it's low risk, Amoxicillin.' They're not going to do that, because they will want you guys to say 'no they're not allergic,' sorry …*
>
> *Site-C, Consultant Anaesthetist*

> *… if you have become familiar with that as let's say someone as an FY2 in maybe acute medical pathway, you then become a registrar and maybe you become a consultant, and then that can be something which you routinely apply in your practice, and I think it's quite important to get, you know, people exposed to it, …*
>
> *Site-C, Research Pharmacist*

An interesting dynamic was noted between experts, champions and generalists, with the former considering the intervention relatively straightforward and easy to implement, but the latter recognising potential limitations due to individuals' beliefs about their own capabilities.

> *I've never yet seen a [penicillin de-labelling] study that's genuinely completely led and delivered by non-allergists. There's always someone right there in the middle of it who's got a lot of expertise, who answers a lot of questions.*
>
> *Site-B, Research Consultant Anaesthetist*

I think confidence is the key, going back to what you were saying information and sort of the correct people who have had the correct training, being able to do that. The worst thing would be that somebody does something and it goes wrong …

Site-C, Consultant Pharmacist

Optimism/pessimism

Generally, HCPs at all sites demonstrated optimism about the intervention during the trial as well as its future implementation into practice. Reasons for this included the proactive and non-invasive nature of the DPC, patient receptiveness, recent publication of national guidelines that align with the study intervention, and wider positive impacts on AMS and reduction in AMR and associated healthcare costs.

Generally, people are quite on board with finding out more, saying that they would want to go into the study.

Site-B, Consultant Anaesthetist

… before the start of this SPACE study, we had the microbiology-led de-labelling protocol, again very similar in what it offers, but the difference is that we proactively seek out patients with labels, so someone you know, goes in on a specific date, searches through the labels and then tries to pick up those who are, rather than a team coming to microbiology when they have no other choice in antibiotics and saying, 'oh what could we do about this?'

Site-C, Research Pharmacist

Beliefs about consequences

Participants at all sites noted concerns about consequences influencing their engagement and ability to implement the intervention. Non-allergy specialists and junior staff indicated that their role and confidence levels would limit their willingness to risk the DPC for fear of adverse outcomes. Similarly, the RPs and nurses expressed that in case of any ambiguity at the risk stratification stage, a full consultation would take place with the allergy specialists before progressing to the DPC.

80% of it is the technical difficulty of working out who actually is appropriate to de-label with a challenge directly, and 20% is the perceived risk around the medical-legal implications.

Site-B, Research Consultant Anaesthetist

I think it would be very unlikely that you would find a nurse who would be prepared without any training to perform risk stratification and then give penicillin when somebody's documented as having a penicillin allergy because, in terms of the risk benefit, all of risk is on them.

Site-B, Consultant Anaesthetist

Memory, attention and decision processes

The decision processes during the study were largely focused on application of the intervention in the form of a penicillin challenge. However, there was awareness that the risk stratification and confirmation or validation of the high-risk status was also in effect an intervention outcome from the study.

… you could jump in your mind actually prescribe and administer and the response as that is an intervention, an actual thing, but you're still making an intervention even for the high-risk patients, I don't know if you agree, but they're still then having the validation of their risk stratification.

Site-C, Consultant Pharmacist

Environmental context and resources

Three levels of environmental context were discussed during the focus groups: macro, meso and micro. At the macro level, participants noted various national resources and policies that were driving the agenda at scale – from shortage of specialists to the national AMS agenda.

… there is a wider educational problem, but in terms of logistics, there aren't enough immunologists out there in the country to provide that sort of service …

Site-C, Research Consultant Immunologist

> *The only model I can foresee working … governance is some of it, … and the BSACI guidelines might help with that … but ultimately it comes down to individuals feeling safe … really well trained … they've done it for a long time and they're working in a small group.*
>
> *Site-B, Research Consultant Anaesthetist*

Wider environmental and contextual barriers included concerns about claims and litigation.

> *Maybe I'm a sceptic but I think everyone's in their silos, I can't ever see other specialist … because … medicolegal …. it's the claim culture … they will want you guys [allergy specialists] to say that …*
>
> *Site-C, Consultant Anaesthetist*

Other initiatives, such as explicit inclusion of allergy history taking into national training and membership programmes, were cited as ways of embedding this into existing professional pathways.

> *GPs … all have to do their MRCGP exam, that's membership of the Royal College of General Practitioners. Concerted lobbying … has now got questions in allergy in their MRCGP exams, so … it focuses the mind.*
>
> *Site-C, Research Consultant Immunologist*

Leveraging existing mechanisms for clinical quality improvement, such as local and national clinical quality indicators (CQUINs), was mentioned:

> *I do wonder if something like a CQUIN could be used as a lever. We've had several CQUINs haven't we? And they do use it as a lever …*
>
> *Site-C, Consultant Pharmacist*

Harnessing changes in the healthcare infrastructure was also raised as an area for consideration to emphasise the wider system impact and resources.

> *The positive spin on that could be the potential amount of money which will be saved if we can de-label a user, but that's a hard sell.*
>
> *Site-A, Consultant Acute Medicine*

> *It's a hard calculation to make and I think something of that grit you'd need to have the system involved. It's not Trust-specific or primary care-specific. You'd have to say 'this is a system-wide issue so the ICB has to be involved and look at where it might be prioritised in their limited amount of funding' and you might be able to make a case or you might not …*
>
> *Site-A, Consultant Infectious Diseases*

The meso-level factors included the use and availability of guidelines, electronic decision support tools and governance frameworks within organisations. The impact of digital systems on documentation, and the general quality of documentation of allergy were noted by Site-C focus group participants as enablers as well as barriers to accurate allergy labelling, within and across care sectors.

> *… some of the other Trusts don't use a micro guide like we do, they use the decision support tool function, and in the decision support tool it forces you down a tree and you do have to say is it an allergy? Has it been confirmed? So, you almost wonder if the actual active role of having to say yes or no, makes you think slightly different to just reading a passive guidance …*
>
> *Site-C, Consultant Pharmacist*

> *… let's say they give a good history of having a specific drug at a specific time and having let's say diarrhoea, right, you are obliged to document that, but the way you document that within the system let's say appears in exact way as you would be documenting anaphylaxis, or Stevens-Johnson or something which can be that contradicts further use of the drug …*
>
> *Site-C, Research Pharmacist*

> *… the most shocking part was really the quality of the documentation of the allergies, so whether that's just general labelling someone as allergic to penicillin, or specific drug, really at all the other information is not there, so I think then that's where really the challenge starts, is you really don't have any confidence in that label …*
>
> *Site-C, Research Pharmacist*

At the micro level, availability of dedicated space (treatment room or clinic), equipment (such as blood pressure monitoring) and medications (for the intervention as well as rescue or supportive medicines in case of AEs) were considered essential to facilitate successful delivery of the intervention. Clinical areas where there was a need to prescribe antibiotics and capacity for close monitoring, such as the AMU or theatres, were reported as facilitators. The timing and value in the context of the patient's care and the clinician's work were also key.

> *… immunology registrars currently, we shadowed him in the routine drug challenge clinic, so he said that what he felt was unless you perhaps need to prescribe antibiotics as a part of the admission you don't really have motivation to de-label, because there's just too much work …*
>
> *Site-C, Research Pharmacist*

> *I can't imagine that every single bedside nurse is going to want to then to start being able to identify risk stratify, you've got so many competing interests there as an outsider looking in for everything at your moment of time, so I can't imagine it's going to go broad sweep across all the nurses at every bedside.*
>
> *Site-C, Consultant Pharmacist*

Social influences

Social influences on patients

In this context, the term 'social influences' refers to interpersonal processes that might cause those involved to alter their thoughts, feelings, or behaviours towards the intervention. We have already seen how such processes were important in many patients' decisions to proceed with the DPC. Most notably this operated through interaction with members of the clinical teams involved in the study and their manner and confidence with which they communicated the intervention to the patient. This form of influence was again cited by focus group participants across each of the sites, for example:

> *It depends on how you handle it, right? If you as a physician are tentative, they pick up on it. Whereas if you come across as being measured and you provide them with evidence – you don't want to be gung-ho but you're being measured and explaining the approach, by and large, most patients would agree. And that is really important, that's that whole sort of health psychology, health behaviour, isn't it? It's that moment of interaction.*
>
> *Site-C, Research Consultant Immunologist*

The role of social influence could cause patients confusion where they may receive variation in clinical opinions. For example, some focus group participants identified the problem of competing social influences acting on the patient.

> *… you've got a lot of different views … you've got clinicians who know an antibiotic has worked in the past, 'so why am I now changing to a penicillin? Great what you've done, document what you've done, it's nothing to do with me' … you're there trying to justify why this needs to happen now and the patient's on board with it as well. And I think at the back of your mind then you've got that worry that this is going to cause a re-labelling because the patient now can see that 'people aren't agreeing in terms of my treatment' and then the patient's belief drops in what you've done as well.*
>
> *Site-A, Research Pharmacist*

> *I've had some patients where I've challenged them there and then and I've said, 'That's not really an allergy, that's just a side-effect,' and had the conversation. And then they will go to another area and someone will ask them about their allergies, so they come to the anaesthetic room, and they'll still say they're allergic to it.*
>
> *Site-C, Consultant Anaesthetist*

This problem was identified repeatedly in relation to patients' GPs, whose judgement many trusted as much if not more than secondary care clinicians. This confirmed the importance of GP buy-in to and adoption of the DPC intervention.

Social influences between staff

Social influences were also identified between professionals working in the sites. In some cases, these had a long history which was seen as predisposing colleagues to support the intervention:

> *What do we think is unique to this institution that may be part of the reason why it's been implemented in the way it has? Site-C, Facilitator Yeah, we didn't have to persuade anybody to join this study, because we've been doing this here for a long time. We're de-labelling now going back perhaps seven, eight years ago.*
>
> *Site-C, Research Consultant Immunologist*

Actively influencing colleagues was also seen as crucial:

> *… we still periodically come to the [acute medical teams] teaching sessions in the morning to say 'hello, we're still doing so many referrals' … I think it's probably just speaking to them … taking time to understand the process, why perhaps making this decision is important, and identifying those people and reaching out to them, so they can then sort of feedback a percentage of their referrals.*
>
> *Site-C, Research Pharmacist*

However, overcoming resistance through peer-to-peer social influence was acknowledged to be challenging, as the following comment from a pharmacist illustrates:

> *… it's not so easy to kind of go against the grain and be like 'no actually I want this patient to have a penicillin for their cellulitis'. But you almost need everyone to be on that page with you to be able to push that through, so going against the clinical team sometimes is difficult and I've felt that resistance. But most of the time you're okay and, you know, people see what you're saying.*
>
> *Site-A, Research Pharmacist*

Despite this, the expertise of pharmacy colleagues was cited as an important source of influence, especially by nurses participating in the focus group discussions.

Emotion

Patients in our sample appeared inclined to play down the emotional significance of agreeing to the DPC, although some relayed they had anxieties initially. However, participants in the focus groups recounted instances where patients had exhibited behaviours that they associated with high levels of stress.

> *I think for some people that have had quite a nasty experience - not necessarily full-blown anaphylaxis – but we do have to take into account when we're bringing them in for a challenge that because they had such extreme symptoms they sort of work themselves up. We've had a couple where, you know, they say, 'Oh I'm starting to feel hot'. All their obs are fine, but their heartrate starts going up and, you know, it is probably stress that's causing them that, because you're giving them something that they think has caused these symptoms. So, I think that plays a part in it.*
>
> *Site-C, Specialist Nurse*

Clearly, emotional associations were seen as being less prevalent among staff although even for these groups, it was noted that allergy labels related to antibiotics evoked more deep-seated risk aversion than was the case in other treatments:

> *There's also a different perception of risk, specifically around antibiotics … we conducted a study a few years ago and showed that for particular groups of drugs … ethics are much more relaxed about giving the drug, even though there's an allergy label. So, opiates and nonsteroidal in particular. It doesn't matter what people say about the reaction. Basically, analysis [shows people] are quite happy to give them, but it doesn't matter how low risk the history sounds for penicillin, just the existence of the label means that they just won't go near it. So, there's a kind of disproportionate anxiety around penicillin.*
>
> *Site-B, Research Consultant Anaesthetist*

These raised anxiety levels were occasionally echoed by study team members:

> *I think the fear still looms at the back of the clinical head that what if something was missed and they end up with an anaphylaxis and what we'll do? And the reassurance again comes back to us that this is the hospital setting, we've got everything ready, it hasn't happened. I always say a little prayer before. [Laughter] Despite our robust plans and algorithms I always resort to my little prayer!*
>
> *Site-A, Consultant Acute Medicine*

Reinforcement

The focus group participants at all sites recognised the importance and need for the intervention to improve AMS and patient outcomes. However, they also acknowledged the extensive change in behaviours, systems and practice that was necessary for implementation, and noted factors that may stimulate and reinforce the change.

Published evidence, incentives and alignment with national initiatives such as specialist society recommendations and guidelines were identified as key determinants of increasing the adoption, spread and sustainability of the intervention.

> *… national toolkit published haven't you about making non-medical prescribers to be able to do this, … there's a national driver to do that, … this SPACE study work … can only help and support and give more confidence to people who are going to be taking this forward, … in a very structured manner with the support and the backup, but there will be potentially other centres who haven't got that infrastructure …*
>
> *Site-C, Consultant Pharmacist*

> *the British Society for Allergy and Clinical Immunology have recently published a guideline for direct Penicillin oral challenge by non-specialist, okay, and this initiative was a collaboration with all the colleges, Royal Colleges, including the College of Paediatrics, Royal College of Physicians, um, Royal College of Surgeons, Pathologists, all the different colleges, it was a joint effort and it's been published so it's there now … systematic review that was published … studies which have used the direct oral Penicillin challenge and shown that it's a very safe procedure …*
>
> *Site-A, Consultant Immunologist*

Organisational policy and governance frameworks were also considered essential to support individual clinician decisions and practices.

> *… if something goes wrong here, another clinician has said they've got a Penicillin allergy, I've completely ignored it and given them Penicillin anyway. So having that framework and guideline so that you're backed by the organisation is absolutely critical …*
>
> *Site-A, Consultant Respiratory Medicine*

Participants noted that recognition of the wider, public health implications of spurious penicillin allergy labelling at a global level would also reinforce the importance of implementing the study intervention.

> *… one of the drivers of antibiotic resistance is this spurious epidemic of Penicillin allergy … there's a Penicillin allergy day designated by WHO … American Academy of Allergy Asthma and Immunology, in public health terms this is huge …*
>
> *Site-C, Research Consultant Immunologist*

Financial implications, in terms of incentives or penalties, resources and cost of services are also mentioned as a way of influencing individual behaviour and organisational change.

> *… they can't get hospital approval … can't get financed … can't find anyone to run the service or they've got the service up and running, but they just can't seem to get any patients into it …*
>
> *Site-B, Research Consultant Anaesthetist*

> *… have to present it in the context of how much more expensive the second line antibiotics there are, how they're then needed for longer … have to do the money saving…*
>
> *Site-C, Consultant Pharmacist*

Good practice suggestions

The focus group participants were very engaged and supportive of the DPC, with all of them agreeing with that this was an important area of AMS. In articulating the challenges and barriers generally, as well as the specific experiences from this study, they suggested areas of good practices as presented below.

Complete and clear communication between primary and secondary care, as well as patient and professional, was identified as one of the main practices to prevent inappropriate PAL as well as successful revision of this after a DPC. This included ensuring adequate patient education and awareness of the differences between medicines intolerance and allergic reactions.

Another area was to raise awareness of the risk stratification and DPC amongst HCPs and embed this in clinical practice. EP and health record systems were mentioned as tools to aid full documentation, help risk stratification and guide clinical decisions. Systems that facilitate (e.g. templates, algorithms and decision support tools) rather than constrain (e.g. no place to record severity or differentiate intolerance in some primary care systems) clinical decision-making were considered to be more likely to be effective.

Participants strongly advocated the need for governance to endorse best practices, such as embedding the principles in local guidelines and underpinned by national policy. Clarity of roles and responsibilities including appropriate escalation or referral pathways and incorporating national commissioning, new pathways and existing quality priority and indicator frameworks were suggested recommendations for embedding the change across the whole health sector.

> *So it is, you know, it hasn't translated into any direct policies or any commissioning frameworks or anything like that but, you know, you can already see that potentially you'd need a really robust business case for a Trust to be able to want to invest in secondary care de-labelling service. But, you know, if you had that in place you can see that how you can then incentivise primary care to do some screening, whether it's through the structure medication reviews, you know, the DES or you could even have a community pharmacy commissioned pathway screening, you know, if we were going down the screening route …*
>
> *Site-A, Commissioner Representative*

> *… if you don't achieve change by gentle persuasion then you then have to come in with some sort of financial stick, and it works …*
>
> *Site-C, Research Consultant Immunologist*

> *… Do a quality priority for the GP, align the two, you've got the whole health economy covered …*
>
> *Site-C, Consultant Pharmacist*

Discussion

The aim of this work stream was to identify the individual and organisational factors that may influence implementation and adoption of the penicillin allergy de-labelling intervention.

Key findings

On the whole, patients demonstrated a sense of trust and belief in the health system as well as the HCP, and this predisposed them to accept the intervention. The risk stratification as low risk meant that for most of our interview sample, the initial labelling as allergic had not been accompanied by severe symptoms. Therefore, patients were amenable to the arguments and reassurances put forward by the study team. Some patients expressed curiosity about their allergy status and others consented primarily as a means of advancing research and patient care. Those who had chronic or recurrent interaction with health care or need for antibiotics were the ones who were beginning to consider

the impact and implications of having a penicillin allergy – for their own treatment outcomes as well as choices that HCPs had to make in the patient's best interest. Again, underpinning each of these motivations and behaviours was an espoused faith in the judgement of medical teams and the security of the hospital environment.

Staff perspectives were notably more complex and nuanced. The value of the intervention was well understood and supported by all those involved in the focus groups. The primary areas of concern related to factors such as the skills, resources and governance required for implementation. For example, a source of some discussion was the initial phase of the intervention in which patients were interviewed, drug histories recorded, and risk stratification undertaken. There was some concern expressed that these activities required more than a checklist approach, and there were differing opinions as to the level and forms of specialist input required.

As with all service changes and innovations, this study uncovered impediments to implementation and highlighted the resources required for routinisation of the new way of working. For patients, the most important predisposing factors appeared to be the assurances of HCPs and the perceived security of receiving the intervention in a secondary care context. For staff involved in implementation, the changes were more substantial and complex to manage. For example, one key area of variation across sites was the extent of allergy specialist involvement in risk stratification. Although non-specialist de-labelling is a key principle of the DPC intervention, allergy specialist input remained an important element of its implementation in each of the three sites. In two of these, there was a general consensus that this input had reduced and that a transfer of responsibility to non-specialists had taken place. However, this was a gradual and incomplete process, and in the third site was not observed to any significant degree.

It is likely that these challenges and points of variation are not entirely reducible to questions of technical expertise but instead appeared to be informed by understandable concerns to minimise risk, both to patients and to staff. In this regard, the study underlines the importance of an organisational plan to enable sustained adoption of the de-labelling service. For example, despite the efforts of the study teams in each site, referral rates remained either low or inconsistent, suggesting either passivity or lack of buy-in from other staff groups. This is perhaps not surprising during the initial phases of intervention testing but would imply the need for an additional cross-organisational focus in the next phase. The limits of the study preclude us from directly investigating the factors influencing these referral rates. For example, they could reflect the pressures faced by those working within healthcare organisations, 'research fatigue' or more specific prioritisation of other activities and demands over allergy de-labelling.

A second element of wider governance highlighted by focus group participants was the reassurance gained from a formal organisational policy and protocol in favour of the DPC intervention. This was felt to be an important means for reducing the perceived risks to staff involved in the de-labelling (i.e. the 'claim culture'), and which would help to mitigate the raised levels of anxiety associated with antibiotic allergies.

Overall, there are some commonalities across the findings from patient interviews and staff focus group discussions, and the overriding sentiments were in support of de-labelling. However, whereas patients experienced the DPC as largely straightforward, staff identified some important implementation determinants – relating to issues of risk, organisation, governance and workforce – for consideration in any future adoption of the DPC intervention.

Comparison to previous research

These findings are similar to recent studies of drug allergy evaluations and de-labelling, which show the importance of accurate allergy history and documentation by clinicians, increasing awareness of allergy de-labelling services amongst HCPs for appropriate referrals, and the need to engage and address patient (and parent/carer) perspectives and understanding of medication/antibiotic allergies.[43,64–66]

In an interview study involving parents of children who underwent an oral penicillin challenge, one of the key themes for being given a PAL was a lack of thorough clinical history, examination and appropriate initial investigation.[64] This was mirrored in our analyses where we identified the harms of having an unchallenged and inappropriate allergy label, including the unnecessary cascade of actions that may follow, such as second-line antibiotic prescribing.

Similar to our findings, the lack of awareness among patients about the benefits of penicillin allergy testing and a lack of certainty among clinicians about criteria for referral, and the need for good communication between primary and secondary care to facilitate accurate medical records and better patient education have been recognised previously.[65]

The potential for hospital-based non-allergy specialists (such as pharmacists) led de-labelling services has been studied in other countries, with similar conclusions,[43] providing evidence that pharmacist's knowledge and transferable skills made them suitably qualified to deliver this type of service, with input from a senior or specialist clinician as needed. Our work has shown that a combination of initial specialist input to set up the training and governance infrastructure, with support from senior non-allergy clinicians, offered appropriate oversight to a de-labelling service delivered that may be delivered by pharmacists or nurses.

Maintaining the accuracy of the allergy history was an overarching theme in the study, emphasising the need for clear documentation and contemporaneous records across multiple and cross-sector health records, underpinned by good communication between the patient and HCPs. However, the role of current electronic health record systems was considered to be more constraining than facilitative. In particular, the functionality of electronic health records to enable HCPs' ability to differentiate and document an intolerance or adverse effects compared to a true allergy was similar to the experience reported in primary care.[67]

This study highlighted the complexities of penicillin allergy de-labelling by non-allergy specialists in acute care settings, and the need for appropriate governance, infrastructure (work systems, equipment, space) as well as and time to risk stratify. Building on similar findings from a previous study, we were able to elicit contextual factors across the three speciality areas and the different organisations.[68] Our findings demonstrate that a clear understanding and management of these complexities and contextual factors can help to implement and establish the intervention although we did not fully elucidate health system models, such as administrative or business support required to sustain such services in the long term.

An intervention development lens

This study suggests that the DPC intervention does not contain any inherent characteristics that would prevent or significantly impede its adoption into practice, and it demonstrated high levels of acceptability, especially among patients. However, as with all service interventions it is likely that some adaptation to local context is required, and the intervention will not be identical in each setting. For example, points of variability might include deciding to focus on therapeutic versus opportunistic de-labelling, determining optimal patient pathways, clear roles and responsibilities for those involved in delivering the intervention, and mechanisms to record and communicate the outcomes of the de-labelling to all stakeholders.

According to established behavioural theories, there are three main requirements of behaviour change: motivation, opportunity and capability.[69] Each of these can be mutually reinforcing and interact to produce a 'behavioural system' which in turn influences receptiveness to new ways of working. An intervention such as the DPC can impact on one or more elements of the behavioural system and these impacts will not always be predictable. Using this as our lens, we can infer from the implementing sites that *motivation* was successfully addressed, especially among the patient group recruited for the study. Future research should extend this to the full range of patient sub-populations, including those with different ethnic and sociodemographic profiles. It will also be necessary to address motivation among more 'distant' actors in the implementation chain, including organisational leaders and professional staff referring to the DPC service. Motivation will also be important for the adaptation of the intervention to local settings so that any obstacles are negotiated rather than treated as reasons to stop the service.

The study also sheds light on issues of *opportunity* and *capabilities*. From the findings, we can postulate some minimum infrastructural requirements for adoption of the DPC intervention, including trained staff, suitable locations, appropriate equipment, access to patients, referral pathways and associated business models. These imply the need for active support of, for example, senior management teams, and those responsible for integrating de-labelling into complex care pathways. Delivery of the DPC and its routinisation into ongoing practice also requires significant levels of initial expertise and capability, albeit these will reduce over time in a context of organisational buy-in and support. This requires flexibility and monitoring to find the optimal blend of core capabilities (and responsibilities) between the immediate de-labelling team and more episodic input from senior and/or allergy-specialist colleagues.

Limitations

The qualitative WS provided rich insights from patients and HCPs involved, with some limitations. First, owing to the study design we could not interview those patients who did not consent to risk stratification or those who declined to participate for various reasons as outlined in *Chapter 2*. It is possible that those patients who declined to be involved in the study may be less receptive to the intervention, thereby biasing our results. Second, the inclusion criteria required interviewees and focus group participants to have English language fluency. Thus, the views of those without English language skills and those with severe mental illness were not considered. Third, the intervention was implemented during the COVID pandemic recovery period. All the patient interviews were conducted via telephone rather than in person as originally planned, and so there was no opportunity to capture non-verbal cues from the interviewees.

Finally, although our fieldwork was confined to the secondary care setting, there was some representation from GP referrers and commissioners in the focus groups. We did not fully elucidate health system models, such as administrative support or business models required to sustain such services in the long term.

Chapter 4 Economic modelling of a direct oral penicillin challenge in penicillin allergy de-labelling

Previous studies have shown that a DPC may be used to remove incorrect PALs in low-risk patients at a lower cost than skin testing while also saving costs of antibiotic medication. However, no previous study has evaluated the costs of all the activities required to identify patients eligible for and willing to undergo the DPC, nor have they evaluated DPC across different patient groups and pharmacist versus nurse-led non-allergy specialist DPC models.

The study found that the full cost of the DPC pathway is larger than that of performing the oral challenge test itself, respectively £940 versus £98–288 per patient. These costs are partly driven by the study protocol and opportunities for efficiency savings exist in adapting any of these different models into routine practice.

The pharmacist-led model investigated at the Birmingham and Oxford study sites would benefit from a shift in staff skill mix that allows administrative staff to substitute pharmacists in performing non-clinical and non-patient-facing tasks. The nurse-led model in Leeds was found to have potential for efficiency improvements in relation to increasing the coverage rate of eligible patients who are approached to undergo risk stratification. Overall, however, the greatest uncertainty and expected return of investment in future research was found in the full-pharmacist-led model demonstrated at Oxford, which while incurring high costs from pharmacists performing activities that do not require clinical specialist training, such as administrative tasks, nevertheless achieved high numbers of DPC and de-labelled patients.

Introduction

The SPACE study investigated a penicillin allergy de-labelling delivered by RPs and RNs at Birmingham and RPs at Oxford, and RNs at Leeds under supervision of non-allergy specialist study consultants. All research staff underwent training in all aspects of the study at a pre-study workshop to standardise procedures. This chapter is aligned with the secondary objectives of the SPACE study, namely to evaluate the potential cost-effectiveness of DPC in 'low risk' patients with a PAL relative to standard of care from the perspective of the NHS and personal social services and identify key areas of uncertainty to inform a future definitive study using value of information analysis.

The specific objective of the economic evaluation was to conduct a cost analysis comparing DPC with current NHS standard care. Although some hospitals offer allergy specialist-led de-labelling services, low-risk patients do not have access to such services in routine practice and therefore in what follows 'current standard care' means no PAL testing service (i.e. do nothing). Therefore, we estimate the costs of delivering the DPC and compare them with the expected cost savings associated with using penicillin for treating or preventing an infection where penicillin is a first-line treatment option following successful de-labelling as opposed to second-line antibiotics in the context of a PAL. Since most patients in the study had their PAL tested on an elective basis, we conducted exploratory analyses to investigate the potential impact of the intervention on the costs of antibiotic use in the community and, for patients attending the haematology-oncology units, the effect on the costs of managing an episode of neutropenic sepsis (NS). We also explored the effect on overall healthcare costs of accounting for potential effects of DPC on LOS amongst patients who underwent therapeutic de-labelling.

Some relevant costs to AMS policy were beyond the scope of this study and not considered in our analyses or only explored in modelling scenarios. The SPACE study was not designed to capture any patient-related outcomes or healthcare-associated infections, for example, MRSA, *C. difficile*, vancomycin-resistant *Enterococcus*, LOS, mortality, risk of wound infections postoperatively and the management of sepsis at the front door. Although re-admission rates and LOS were not measured in the study, we consider the potential economic implications of conducting further research to measure these outcomes.

The next two sections describe the methods and data sources used for estimating the costs of the DPC patient pathway in the SPACE study relative to current standard care, modelling healthcare costs beyond the end of the SPACE study follow-up based on evidence from the literature and assessing the value of future research. The *Results* section presents the results of the economic and value of information analysis. *Discussion with local managers* presents the findings of discussions held with local managers about the evidence that would be most relevant for planning and informing the adoption of DPC in routine practice and *Discussion* concludes with a discussion of our findings. This study is being reported according to the Consolidated Health Economic Evaluation Reporting Standards reporting guidelines (see *Report Supplementary Material 3*).

Methods

Mapping of treatment pathways

Interviews were held with RPs and RNs delivering the SPACE study and consultants from three specialties (presurgical, haematology-oncology and AMU) to map the DPC intervention and current standard of care pathways at the three study hospital sites. The interviews took place between March 2022 and June 2022 and involved three RPs (one at Birmingham, two at Oxford), two RNs (Leeds), one Consultant Oncologist (Leeds), three Surgical Consultants (one at each of the three sites) and two ID/Microbiology Consultants (Birmingham and Leeds). An interview with the ID Consultant at Oxford could not be arranged after three requests.

The interviews were structured in three parts. The first part asked the interviewees to describe the current standard of care patient pathway for PALs in each of the three specialties at their respective hospitals, including the points in the pathway at which a PAL may be scrutinised by HCPs. The second part of the interview focused on the DPC and how it might impact on clinical management. The third part of the interviews involved RPs and RNs delivering the SPACE study and focused on human and material resources required to deliver DPC. Follow-up questions were circulated by electronic correspondence to individual interviewees to seek clarifications following the interviews.

The Clinical Pharmacists in Birmingham occasionally undertake DPC for 'low risk' patients as part of routine clinical care from the AMS service; this is based on a peer review by the AMS team rather than an approved Trust Level protocol. The Oxford site has a local protocol for 'therapeutic de-labelling' employed by the AMS team for patients deemed 'low risk' but participants identified as eligible for the SPACE study would not have been approached in routine clinical practice. While the three sites have a regional specialist drug allergy service, this is outpatient based and does not run an urgent inpatient service for penicillin allergy de-labelling. Since 'low-risk' patients with a PAL included in SPACE would not have received DPC as part of routine clinical care, nor is there the capacity in allergy services to routinely offer DPC for these patients, the relevant comparator for evaluating the DPC intervention in our subsequent analysis was 'no testing and manage according to the PAL'.

Development of the direct oral penicillin challenge pathway model

Interviews with clinical staff delivering the SPACE study and consultant specialists at the three study sites revealed that any potential effect of DPC was likely to be limited to altering the patient management pathway of 'low-risk' patients successfully de-labelled. This allowed us to simplify the analysis to assume any differences in outcomes would be limited to patients with a negative DPC result. *Figure 4* presents a decision tree depicting the impact of DPC.

Details of the patient pathway illustrated in *Figure 4* are described in detail in *Chapter 2*. Briefly, admitted adult patients are screened to identify those who may be eligible for the intervention and approached for consent to undergo risk stratification, which involves taking a comprehensive allergy history and reviewing the patients' medical records. Some of those identified as eligible may be unreachable or approached but decline to be assessed. After risk stratification, patients deemed to be 'low risk' are offered a DPC. For participants from the AMU/IDU that have been discharged, of those in the presurgical group or from the haematology-oncology unit this is conducted on a separate visit. For consenting AMU/IDU inpatients, it is conducted on the same day. High-risk patients are evaluated and those meeting the BSACI referral criteria have an outcome letter recommending evaluation by the allergy specialist sent out to their GP for onward referral. Patients eligible for DPC after risk stratification were not always offered DPC immediately due to time pressures, NHS surgery waiting lists, or if patients became clinically unstable (e.g. withdrawn); these patients

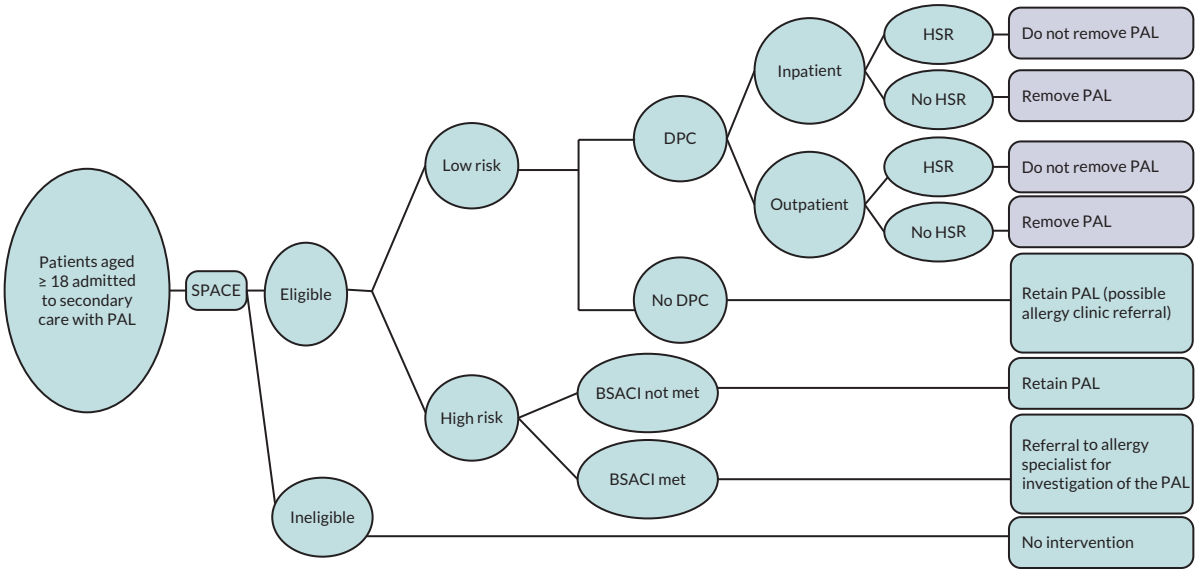

FIGURE 4 Decision tree of SPACE intervention. Circles represent chance events in the DPC pathway moving from identifying an adult patient with PAL, on the far left of the pathway diagram, through assessment of eligibility, risk stratification and, for patients deemed low risk, the probability of undergoing DPC or not undergoing DPC as inpatient or outpatient with associated outcomes, on the far right, of de-labelling ('PAL removal') or not de-labelling ('Do not remove PAL'). Purple shaded boxes reflect outcomes that would be altered by DPC relative to outcomes that would have been observed under the counterfactual standard of care pathway. In the present analysis, outcomes refer to costs of DPC and antibiotic costs in the main analysis. Reproduced with permission from Bestwick *et al.*[70] 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.

retained their PAL and were not referred to the allergy clinic for de-labelling. Those who do undergo DPC either in an inpatient or outpatient basis, or before or after surgery, would be followed up until day 5 to ascertain the outcome of the DPC. Any emergent AE or SAE was investigated by the pharmacist, study consultant and PI and the patient de-labelled if the events were deemed not to represent a HSR; otherwise, the PAL was not removed.

Inferring the effects of de-labelling on antibiotic costs at the point of de-labelling

The consequences of de-labelling would vary depending on the clinical setting. Patients in AMU/IDU undergoing 'therapeutic de-labelling' and who were not already on a first-line penicillin-containing antibiotic would have immediate clinical benefit. For example, de-labelling these patients permits them to be switched from less preferable second-line therapy (the counterfactual regimen that would have occurred in the absence of DPC) to the first-line penicillin-containing treatment. Similarly, for patients in the presurgical group, if the first-line prophylaxis contained penicillin they would now be able to receive this instead of a second-line antibiotic.

However, many patients in the SPACE study underwent DPC following their surgery due to NHS capacity constraints amidst the COVID-19 pandemic and therefore did not realise the immediate benefits of removing an incorrect PAL.

Haematology-oncology patients also did not realise the immediate benefit of a successful DPC. However, many of these patients undergo specialist treatment which makes them immunocompromised and at increased risk of infection, including NS, a life-threatening scenario. A successful DPC would enable them to receive penicillin treatment for future NS events. For the presurgical and haematology-oncology patients, we explored the antibiotic cost savings associated with using penicillin versus alternative antibiotics in the context of presurgical prophylaxis and possible NS respectively, as per local Trust protocols in the scenario of a patient with and without a PAL (following DPC). This is described in the following sections.

Acute medical/infectious diseases unit patients

Patient demographics and details of antibiotics used post DPC including names, dose, route of administration, number of doses, and the nature of infection were captured. The local hospital guidelines for managing patients with PAL were

also used to infer the treatment that would have been given for the recorded infection if the PAL was not removed. These data were then used to compare the cost of using penicillin antibiotics in the de-labelled patients versus the cost of alternative antibiotics in the context of PAL if the patient was not de-labelled.

Presurgical patients

All participants in the presurgical setting de-labelled prior to surgery were analysed retrospectively for antibiotic prophylaxis. A cost analysis was conducted for antibiotic use as per local Trust guidelines in the context of PAL and following the removal of PAL status. Details of the type of surgical procedure were factored into this analysis as the surgical site drives the choice of antibiotic administered.

Effects of de-labelling on antibiotic costs in subsequent hospital episodes (haematology-oncology patients)

For the haematology-oncology patients, the implications of de-labelling were considered in a hypothetical scenario of NS, chosen for its common and serious occurrence. The best source of published evidence is the National Institute for Health and Care Excellence (NICE) 2012 Guideline on prophylactic strategies for NS for adult cancer patients who are receiving outpatient chemotherapy.[71] The economic evaluation that informed the Guideline conducted separate analyses for

- adult patients with Hodgkin lymphoma (receive full-dose chemotherapy throughout) and
- adult patients with a solid tumour or non-Hodgkin lymphoma (reduced chemotherapy dose following one NS episode and discontinue after a second NS episode).

Advice from study consultants indicated that these patients are relatively less complicated and are managed with different prophylactic regimens from those used for other cancers, for example, acute myeloid leukaemia and chronic lymphocytic leukaemia or myeloma. Since modelling the heterogeneity of the haematology-oncology patient population was beyond the scope of the SPACE study, and in view of the lack of systematic evidence on other types of cancer, we adopted the model of disease course of non-Hodgkin lymphoma patients that informed the NICE guideline as an example for the potential benefits of DPC. Therefore, the actual diagnosis of de-labelled patients was not considered in this hypothetical analysis for patients recruited from haematology-oncology settings in the SPACE study, whose inclusion criteria were not restricted to a particular cancer type.

The risk of NS for patients receiving chemotherapy is sometimes managed by giving patients prophylaxis. We have calculated the expected number of NS events over one course of six 21-day cycles of chemotherapy for newly diagnosed non-Hodgkin lymphoma patients who also received granulocyte-colony stimulating factor prophylaxis to be 0.66. This was derived by accounting for the increased NS risk after having a first NS event and the higher risk of NS with the first cycle (National Collaborating Centre for Cancer, UK 2012).[71] We apply this quantity to the unit costs(see *Report Supplementary Material 3*) toderive per-patient cost differences of NS antibiotic use for haematology-oncology patients who are de-labelled. Due to the hypothetical nature of this element, results are only presented in *Report Supplementary Material 3*.

Modelling the effects of de-labelling on antibiotic costs in subsequent primary care episodes

As many patients were de-labelled on an opportunistic basis, that is not 'therapeutic de-labelling', they would only realise the benefit of de-labelling on subsequent episodes of care. Since primary care accounts for the largest share of antibiotic consumption at approximately 70% of antibiotic prescriptions,[72] we modelled the effect of de-labelling on the expected antibiotic prescriptions by general practitioners for the SPACE patient cohort over the 12-month following discharge from their initial hospital admission or episode when the DPC took place (see *Report Supplementary Material 3*). Due to the hypothetical nature of this element, results are only presented in the *Report Supplementary Material 3*.

Data collection and sources

Intervention costs

The costs of training staff and delivering the DPC, including time, consumables, and medications were measured. These costs were identified in the interviews with the RPs and RNs delivering the SPACE study at the three study sites. Based

on these interviews, a questionnaire was designed to quantify time input by senior research staff and all HCPs involved in delivering the DPC at the three study sites (see *Report Supplementary Material 3*). The questionnaire was divided into multiple domains to capture time inputs for training, identification and screening patients, risk stratification and DPC. For the purposes of costing, we used a matrix to map individual inputs into the different steps in the DPC pathway for the purposes of costing as a function of their respective title, grade and experience.

The costs of staff time inputs were evaluated using pay scale data published by the PSSRU 2021–2.[73] The costs of the DPC test consumables were obtained from SPACE study financial records. DPC drug challenge costs were based on electronic market information tool (eMIT) database costs for an amoxicillin single dose of 500 mg and 250 mg amoxicillin twice a day for 3 days. A similar but an individualised approach was employed for 'therapeutic de-labelling' to determine antibiotic costs. The cost of a urine pregnancy test was also included for female participants aged 18–55 years of age who underwent DPC using drug acquisition costs obtained from the finance department. A standard cost for emergency equipment for the management of anaphylaxis was considered, including a nebuliser device, medications including salbutamol nebules, antihistamines, adrenaline injection and hydrocortisone but none of these medications were actually used for study participants at any of the three sites. No account was made for the use of temperature probes, or blood pressure machines, which were provided by each Trust but would have negligible costs. *Table 14* presents unit costs used to value resources consumed in delivering the DPC intervention.

Where available, antibiotic costs were calculated using eMIT. For the NS scenario, not all antibiotic costs were available on eMIT and therefore British National Formulary NHS indicative prices were used for all antibiotics in this scenario.

We estimated the opportunity costs of staff attending training workshops on delivering DPC as part of the SPACE study. In addition, we included the opportunity costs of healthcare staff (a senior pharmacist and allergy specialist)

TABLE 14 Unit costs of SPACE resource inputs

Item	Definition	Unit cost (£)	Source
Training			
Instructor time, senior RP	Hourly, Band 8a	73	Jones and Burns[73] www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ (accessed 15 January 2023)
Instructor time, allergy specialist	Hourly, Senior Consultant	123	
Staff time delivering SPACE			
RP	Hourly, Band 8a	73	Jones and Burns[73] www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/ (accessed 15 January 2023)
Senior RN	Hourly, Grade 6	51	
Data manager	Hourly, Band 4	35	
Allergy specialist	Hourly, Senior Consultant	123	
Consultant managing patient	Hourly, Senior Consultant	123	
DPC tests consumables			
Medications for prolonged DPC	500 mg Amoxicillin STAT ± 250 mg Amoxicillin BD for three days	0.140	www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [accessed 10 November 2022 (e-MIT database)]
Medications for therapeutic DPC	500 mg PO Amoxicillin STAT	0.025	
Pregnancy test	One test kit	0.69	NHS supply chain catalogue 2022 https://my.supplychain.nhs.uk/catalogue (accessed 5 January 2023)

delivering the training workshops to healthcare professionals delivering the DPC. We excluded the costs of training from our main analysis, to reflect the idea that the knowledge acquired from training in DPC would last for several years over which the opportunity cost of training would be divided over a large number of de-labelled patients by trained nurses or pharmacists to become negligible. In scenario analysis, we assume instead that the human capital investment generated by the training would have a productive life of 2 years, to obtain an annual user cost assuming a 5% annual discount rate, in line with methods used to value His Majesty's Treasury capital investment projects.

Costs of antibiotic medication use at the index hospital admission

Costs savings associated with antibiotic use in 'therapeutically de-labelled' patients were determined by the difference in costs between the antibiotic regimen the patients were due to receive at the time of screening and the costs of the first-line antibiotic regimen to which they were switched following de-labelling. The actual observed patient pathway is dynamic with regular antibiotic reviews and medication adjustments according to changing clinical presentation. However, the counterfactual pathway utilised for comparison costing purposes was derived from the local guideline according to the patient's initial clinical indication alone.

Cost savings in de-labelled presurgical patients were inferred based on the local hospital guidelines of the respective site for prophylactic management of the surgery they were listed for, with and without PAL.

Costs of antibiotic medication use in subsequent hospital admissions (only for haematology-oncology patients)

The unit costs of antibiotic treatment of a subsequent episode of NS in individual patients admitted to the haematology-oncology units were derived according to the local hospital guidelines at the three study sites for patients with and without PAL and expert input (see *Report Supplementary Material 3*). The antibiotic costs for NS treatment are on average £133 more costly for patients with a PAL compared to those without. In our calculations, we assume that each haematology-oncology patient has a mean number of 0.66, which implies that each de-labelled haematology-oncology patient would have an average NS antibiotic cost saving of £88.23.

Scenario analysis: costs of antibiotic medication use in subsequent episodes of general practitioner attendance (for all patients)

Cost savings of removing a PAL in the 12-month period after de-labelling were calculated from published estimates on the excess use of antibiotics and the increased share of penicillin among antibiotic classes used in primary care for those patients with a penicillin allergy record[4] (see *Report Supplementary Material 3*). This resulted in an estimated antibiotic cost saving in primary care of not having a penicillin allergy record of £2.38 per patient per year.

Model-based extrapolation

In order to assess the potential impact of DPC beyond the end of patient follow-up in SPACE, we systematically searched the literature for economic modelling studies of DPC with analytical time horizons beyond discharge from the index admission. We found no studies that measured patient health-related quality of life or survival outcomes and only one relevant study using published data from a Western European country setting. Sousa-Pinto *et al.*[74] conducted a cost analysis of DPC in a European outpatient setting using a simple algebraic model populated with data identified from a review of the health service research literature. They reported a net monetary benefit (i.e. cost savings) per 'low risk' patient of £4813 (at year 2020 exchange rates) over 5 years, from reduced hospital re-admissions and antibiotic use, LOS, and outpatient visits in patients with a PAL. We adapted this analysis using more recent published data from the UK, which we identified from a separate systematic review of costs of PAL conducted as part of a related project (Allergy Antibiotics and Microbial Resistance, NIHR-funded 'ALABAMA' study, unpublished).

Table 15 presents the parameter estimates of the different resource use-related events in our model-based extrapolation of costs. Since we could not find any new evidence on the number of subsequent GP contacts per patient per year over 4.5 years avoided by PAL removal, we used the same estimate as that in the study by Sousa-Pinto *et al.*[74] evaluated at UK unit costs (PSSRU 2021) with a 3.5% annual discounting rate as recommended by NICE guidelines. The same applied to the 12-week re-admission relative risk ratio, which was derived from a prospective matched cohort of all patients admitted to a Dutch hospital between 2013 and 2014.[76] Since Office of National Statistics (ONS) data routinely report hospital re-admission rates up to 30 days, we used the 4- to 12-week re-admission rate ratio reported in the study by van Dijk *et al.* to convert the ONS re-admission rates to 90 days.[76]

TABLE 15 Parameters for extrapolation of costs of DPC

Parameter	Point estimate	Distribution	Central tendency and dispersion parameters	Notes
Prevalence				
Eligibility	0.47	Beta	alpha: 1055 beta: 1202	Value in whole SPACE study cohort; analyses were based on subgroup specific values
Approach rate (coverage)	0.61	Beta	alpha: 643 beta: 412	Out of those eligible in whole SPACE study cohort; analyses were based on subgroup specific values
Consent and risk stratified	0.42	Beta	alpha: 270 beta: 373	Out of those approached in whole SPACE study cohort; analyses were based on subgroup specific values
Low risk and undergoes DPC	0.47	Beta	alpha: 126 beta: 144	Out of those consented and risk stratified in whole SPACE study cohort; analyses were based on subgroup specific values
De-labelled	0.97	Beta	alpha: 122 beta: 4	Out of those DPC tested in whole SPACE study cohort; analyses were based on subgroup specific values
Resource use quantities				
Mean annual number of GP contacts avoided per de-labelled patient over 4.5 years	3.052	Normal	Mean: 3.052 SE: 0.375	Mean difference in annual number of GP contacts between primary care patients with a PAL and patients without a PAL matched for age, gender and follow-up period from electronic medical records in Utrecht over a median 4.5 follow-up[75]
12-week re-admission rate: de-labelled patients	0.16	Fixed	N/A	The percentage of emergency re-admissions to any hospital in England occurring within 30 days of the most recent discharge from hospital, HES (reporting period 1 April 2021–31 March 2022), extrapolated to 90-day re-admission using the ratio of 12-week to 4-week re-admission rate reported by van Dijk *et al.*[76]
Relative risk ratio of 12-week re-admissions: PAL vs. de-labelled	1.28	Log normal	Mean: 0.25 SE: 0.08	12-week relative risk ratio of hospital re-admission of patients with PAL vs. without PAL[76]
Mean LOS days avoided by de-labelling vs. PAL (index admission and re-admissions)	0.19	Fixed	N/A	Calculated based on data from *table 6* in Powell *et al.*[19]
Unit costs				
Screening	8–18	Normal	Mean: 8–18 SE: 0.17–0.37	Range of mean unit cost across the three study sites; SE derived from individual patient REDCap data at Birmingham and Oxford sites (see *Table 18*). As Leeds did not collect these data, its SE was imputed using the coefficient of variation in the respective Birmingham and Oxford data
Approach	10–33	Fixed	NA	Range of mean unit cost across the three study sites
Risk stratification	52–217	Normal	Mean: 52–217 SE: 0.51–1.13	Range of mean unit cost across the three study sites; SE derived from individual patient REDCap data at Birmingham and Oxford sites (see *Table 18*). As Leeds did not collect sufficient data, its SE was imputed using coefficient of variation in the respective Birmingham and Oxford data
DPC	84–282	Fixed	N/A	Range of mean unit cost across the three study sites
De-labelling	13–92	Fixed	N/A	Range of mean unit cost across the three study sites

TABLE 15 Parameters for extrapolation of costs of DPC (*continued*)

Parameter	Point estimate	Distribution	Central tendency and dispersion parameters	Notes
Cost of hospital (re) admission	2634	Fixed	N/A	weighted average for the non-elective admission categories, from National Schedule of NHS costs FY 2020–1 www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/ (accessed 10 October 2022)
Cost of per excess bed-day	286	Fixed	N/A	Average of HRG cost for APC days exceeding trim point for each HRG, 2019 National Tariff
Cost per GP contact	28	Fixed	N/A	Cost per GP visit[73]
Prescription costs	31	Fixed	N/A	Prescription costs per GP visit[73]

HRG, Healthcare Resource Group; SE, standard error.

The association of a penicillin allergy record and the LOS in a spell was estimated by Powell *et al.*[19] in all adult or paediatric patients admitted to a medium size hospital in Truro and prescribed antibiotics over the period April 2016–March 2018, using log-normal regression analyses adjusting for age, gender, comorbidity and type of infection. At a mean LOS of 3.4 days (derived from dividing the reported 90,938 total annual LOS days at their hospital by half their 53,408 total spells over their 2-year study period) and patients with penicillin allergy records accounting for 15% (8423 out of 53,408) of all annual spells, their estimated 5.5% increase in spell LOS with a PAL can be translated into an excess bed-days associated with a PAL ΔLOS_{PAL} using the following equation:

$$\Delta LOS_{PAL} = 0.055 * \frac{3.4}{1 + 0.055 * 0.15} = 0.19\,days \quad (1)$$

At the £286 average Healthcare Resource Group (HRG) cost per APC day exceeding the trim point across HRGs in the 2019 tariff used by Powell, the excess bed-days ΔLOS_{PAL} amounts to £53.11 excess costs due to a penicillin allergy record. This figure was applied with a negative sign to therapeutically de-labelled patients from AMU/IDU and presurgical patients de-labelled before surgery to account for the cost savings associated with removing a PAL.

In our extrapolation analysis, the reduction in the costs associated with the LOS of the index admission spell and the costs of re-admissions only applied to patients who underwent therapeutic de-labelling (a subset of AMU/IDU patients) and patients who were de-labelled before surgery. All other cost impacts, that is, the reduction in LOS of any 90-day re-admissions and the costs of general practitioner visits and associated prescriptions costs over the 4.5 years following discharge applied to all patients. We omitted in this analysis the estimated antibiotic cost savings associated with therapeutic de-labelling, presurgical patients delabelled before surgery, NS in haematology-oncology patients, and antibiotic medication use in primary care over 12 months after discharge, described in *Inferring the effects of de-labelling on antibiotic costs at the point of de-labelling*.

In addition to sampling distributions for the resource use quantities in *Table 15*, the probabilistic analysis (see *Value of information analysis*) included the sampling distributions for the cost associated with the variability across patients in the time spent during the screening and risk stratification steps and from the probabilities of patients progressing through the DPC steps from screening to DPC to de-labelling in the simultaneously random sampling.

Sensitivity analyses: intervention costs

We investigated the sensitivity of our results to different scenarios for the performance of DPC. We analysed the variation of costs of DPC as a function of the coverage rate, that is, the proportion of invited patients to undergo risk stratification out of those eligible. We also investigate the effect on the costs of DPC of the following assumptions:

1. Administrative and data manager support were available at Oxford.
2. Optimisation of the Birmingham model by Grade 6/7 RNs undertaking the identification and screening off the Senior RP.
3. Screening and day 5 follow-up incur zero additional costs on existing services.

Statistical and probabilistic analysis

Results of the costs of delivering DPC are presented alongside their associated 95% CrI based on 1000 random samples of the probability of patients progressing through the DPC steps from identification though risk stratification to undergoing DPC and being de-labelled. Results for the model-based extrapolation are also presented in terms of the probability that DPC results in cost savings to the NHS using probabilistic sensitivity analysis.

Value of information analysis

We calculated the expected value of conducting a longitudinal study to investigate the potential impact of DPC on healthcare resource use and costs of the intervention, which in our model results from outcome differences in patients who were de-labelled relative to what would have occurred if they had retained their PAL. This analysis used an EVPI approach to measure the value of conducting further research in terms of overall cost savings to the NHS net of DPC costs (net benefit) in the presurgical SPACE study patient cohort.[77] To extrapolate the value of the research to the UK as a whole among low-risk presurgical patients who need penicillin, we use data from the DALES study, which surveyed 213 NHS hospitals.[78]

This analysis does not take into account the value to patients in terms of health-related quality of life or survival, nor the public health benefits from achieving AMS goals. Instead, it provides a lower bound estimate of potential benefits in terms of cost savings generated to the NHS by DPC in the annual incident cohort of presurgical patients whose benefits are measured over a time horizon of 4.5 years following DPC.

Results

Penicillin allergy label testing

As the SPACE study did not measure patient outcomes, we could not estimate the effectiveness or cost-effectiveness of DPC as originally intended in the study protocol. The following analyses therefore are based on the impact of the intervention on healthcare costs alone.

According to data prospectively recorded on REDCap, screening of participants took an average of 6 minutes (*Table 16*), which matched the mean estimates provided by study sites in their retrospective staff time input questionnaires. On the other hand, the time taken to complete the documentation of risk stratification varied between a mean of 90 minutes in Birmingham and 19 minutes in Oxford which may reflect differences in the activities included in the recorded timings at each site rather than actual differences in performing the risk stratification itself. Our subsequent results were based on the staff time input questionnaires completed by the study sites, which detailed the different activities involved in DPC and used the REDCap data to infer sampling uncertainty in our cost analysis below using the coefficient of variation from Birmingham and Oxford.

Figure 5 presents the DPC models in each of the three study sites, according to the cost of the different staff time in each of the screening, risk stratification, DPC and de-labelling steps as well as the administrative and logistical activities occurring in between these intervention steps.

TABLE 16 Time taken to complete the data collection recorded on REDCap (minutes)

	Birmingham		Leeds		Oxford	
Phase	***N***	**Mean (SD)**	***N***	**Mean (SD)**	***N***	**Mean (SD)**
Screening	685	6.3 (3.4)	3	10.0 (0)	466	5.6 (4.4)
Risk stratification	90	51.4 (30.7)	14	14.1 (13.4)	76	19.0 (5.2)

SD, standard deviation.

Note
Costs were used to account for sampling variability in Birmingham and Oxford and impute variability in Leeds based on coefficient of variation (mean/SD). Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

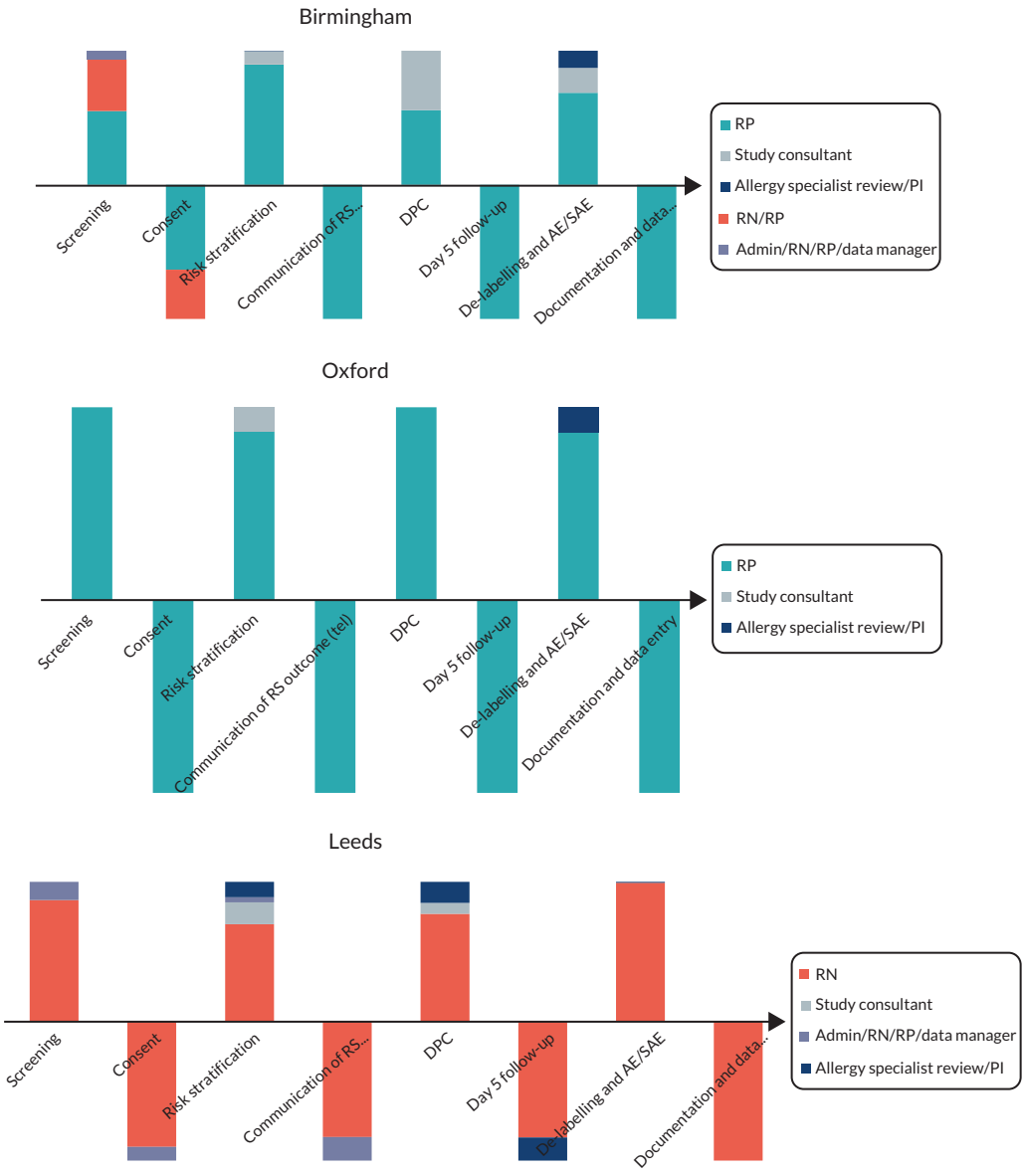

FIGURE 5 Direct oral penicillin challenge models in the three study sites by costed staff inputs (share in cost of each activity). Note: Time spent in documentation and data entry after deducting research-related time, were negligible and had therefore zero associated costs. Reproduced with permission from Bestwick *et al.*[70] 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.

Birmingham

The total opportunity costs of time devoted by staff to receiving training in delivering DPC was £7794 (*Table 17*). Costs of staff time delivering DPC was £68,263, inclusive of training costs. The cost of RPs delivering DPC was £47,187, and that for RN time was £9029.

Time spent in the screening stage accounted for the largest proportion of all staff time involved in DPC (see *Report Supplementary Material 3*). Screening activities in combination with consent at Birmingham accounted for the largest share of total non-training costs at 38% (22,707/60,046; *Figure 6*). Combined with consent they amounted to 38%. Risk stratification and DPC respectively constituted 32% and 22% of non-training costs.

While DPC costs £288 per patient tested, the costs per tested patient increased to £1209 when accounting for staff time inputs required to identify patients through screening and risk stratification (*Table 18*). When all costs including pre-DPC and follow-up are included, the cost per patient screened (i.e. those with a PAL) at Birmingham was £76.

TABLE 17 Costs of staff inputs for SPACE intervention steps (in £) at Birmingham study site

	RP	Study consultant	RN	Admin/data manager	Allergy specialist	Total
Training[a]	5037	1476	408	873		7794
Screening	7858		5490	933		14,281
Consent	5329		3097			8426
Risk stratification	17,551	1927	34		62	19,574
Communication of RS outcome via telephone	1034					1034
DPC	7531	5997				13,528
Day 5 follow-up	1144					1144
De-labelling and AE/SAE	1703	461			318	2482
Total	47,187	9861	9029	1806	380	68,263

a Training costs refer to the opportunity costs of attending training and the staff time spent by instructors training other staff. Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

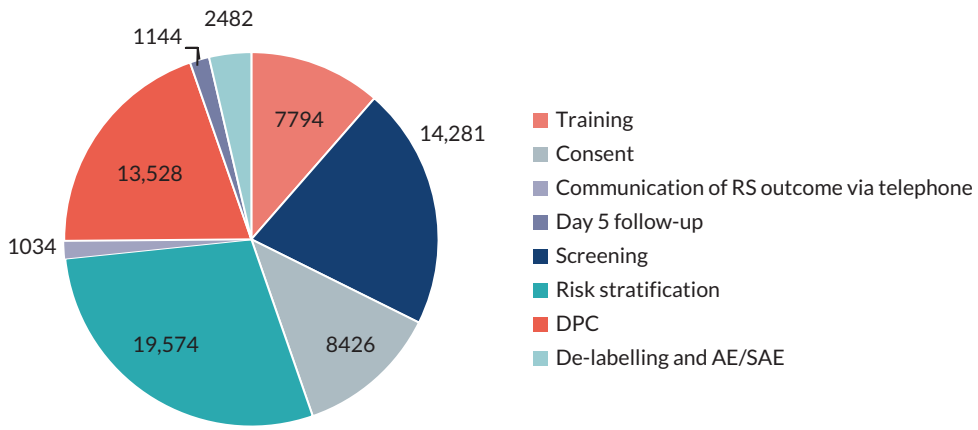

FIGURE 6 Staff cost shares for SPACE delivering activities at Birmingham study site (£). Reproduced with permission from Bestwick *et al.*[70] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, 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.

TABLE 18 Staff costs of SPACE intervention at Birmingham site (£)

	Total cost at each step (a)	Number of patients undergoing each step (b)	Cost per patient at each step (a/b)	Total cumulative costs at each step	Total cumulative cost per patient at each step (c/b)	Total cumulative costs per screened patient (d)
Screening/ identification	14,281	796	18	14,281	18	18
Approached	8426	256	33	22,707	89	29
Risk stratification[a]	20,608	93	222	43,315	466	54
Direct oral challenge	13,528	47	288	56,843	1209	71
De-labelling and follow-up	3626	45	81	60,469	1344	76

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TABLE 19 Costs of staff inputs into delivering SPACE intervention steps (in £) at Oxford site

	RP	Study consultant	RN	Admin/data manager	Allergy specialist	Total
Training[a]	1460	1476			408	3344
Screening	4434					4434
Consent	3279					3279
Risk stratification	11,344	1650				12,994
Communication of RS outcome via telephone	468					468
DPC	7623					7623
Day 5 follow-up	858					858
De-labelling and AE/SAE	3103				462	3565
Total	32,569	3126	0	0	870	36,565

a Training costs refer to the opportunity costs of attending training and the staff time spent by instructors training other staff. Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

Oxford

The total opportunity costs of time devoted by staff to receiving training in delivering DPC was £3344 (*Table 19*). Costs of staff time delivering DPC was £36,565. The cost of RPs delivering DPC was £32,569 and there was no nurse or admin/data manager time input, as these activities were performed by the RPs and included in their costs of delivering the intervention at Oxford themselves (under the 'research pharmacist' column in *Table 19*).

Time spent in the risk stratification stage accounted for the largest proportion of all staff time involved in DPC (see *Report Supplementary Material 3*). Risk stratification activities at Oxford accounted for the largest share of total non-training costs at 39% (12,994/33,221; *Figure 7*). Screening combined with consent amounted to 23%. Oral challenge constituted 23% of non-training costs.

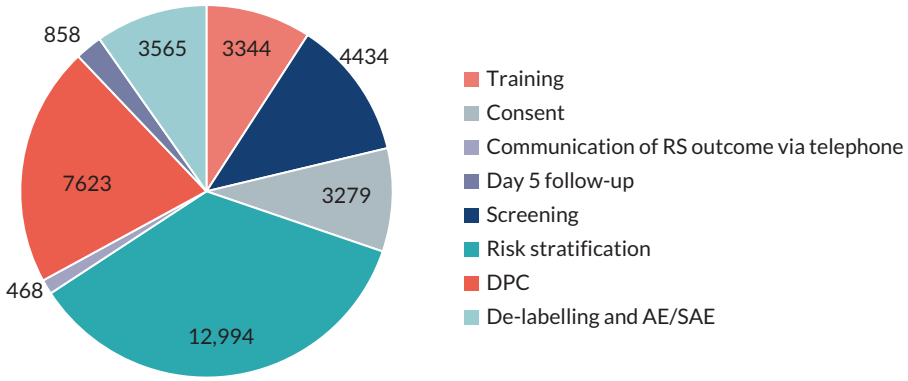

FIGURE 7 Staff cost shares for SPACE delivering activities at Oxford site (£). Reproduced with permission from Bestwick *et al.*[70] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, 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.

TABLE 20 Staff costs of SPACE intervention at Oxford site (£)

	Total cost at each step (a)	Number of patients undergoing each step (b)	Cost per patient at each step (a/b)	Total cumulative costs at each step (c)	Total cumulative cost per patient at each step (c/b)	Total cumulative costs per screened patient (d)
Screening/ identification	4434	472	9	4434	9	9
Approached	3279	182	18	7713	42	16
Risk stratification[a]	13,462	77	175	21,175	275	45
Direct oral challenge	7623	47	162	28,798	613	61
De-labelling and follow-up	4423	46	96	33,221	722	70

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While the DPC itself costs £162 per patient tested, the costs per tested patient increase to £613 when accounting for all the staff time inputs required to identify patients through screening, consent and risk stratification (*Table 20*). When all costs including pre-DPC and de-labelling and follow-up are included, the cost per patient screened (i.e. those with a PAL) at Oxford costs £70.

Leeds

The total opportunity costs of time devoted by staff to receiving training in delivering DPC was £3642 (*Table 21*). Costs of staff time delivering DPC was £24,691. There was no RP input and therefore cost of delivering DPC, while the cost of RN time inputs was £19,301.

Time spent in the screening stage accounted for the largest proportion of all staff time involved in DPC (see *Report Supplementary Material 3*). Screening activities at Leeds also accounted for the largest share of total non-training costs at 38% and the largest across study sites (7947/21,049; *Figure 8*). Combined with consent they amounted to 59%. Risk stratification and oral challenge respectively constituted 22% and 15% of non-training costs.

TABLE 21 Costs of staff inputs into delivering SPACE intervention steps (in £) at Leeds site

	RP	Study consultant	RN	Admin/data manager	Allergy specialist	Total
Training[a]		1476	1932	234		3642
Screening			6909	1038		7947
Consent			4076	444		4521
Risk stratification		729	3241	173	513	4656
Communication of RS outcome via telephone			69	14		83
DPC		248	2422	474		3144
Day 5 follow-up		0	221	44		266
De-labelling and AE/SAE		0	430	3	0	433
Total	0	2453	19,301	2425	513	24,691

a Training costs refer to the opportunity costs of attending training and the staff time spent by instructors training other staff. Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

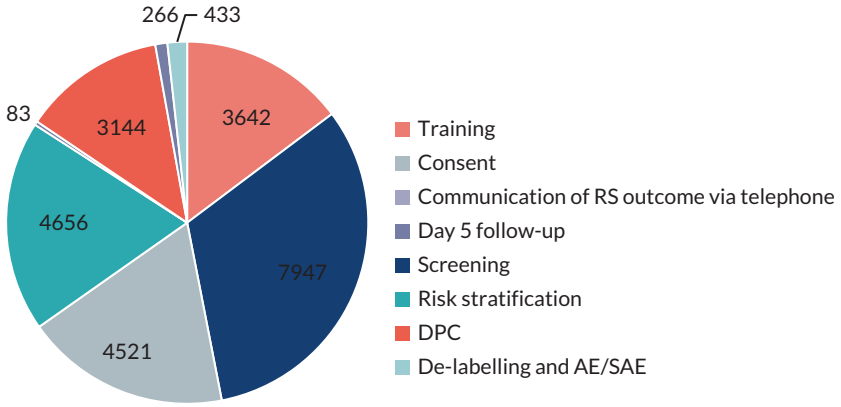

FIGURE 8 Staff cost shares for SPACE delivering activities at Leeds site (£). Reproduced with permission from Bestwick *et al.*[70] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, 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.

While the DPC itself costs £98 per patient tested, the costs per tested patient increased to £636 when accounting for all the staff time inputs required to identify those patients through screening, consent and risk stratification (*Table 22*). When all costs including before DPC and de-labelling and follow-up are included, the cost per patient screened (i.e. those with a PAL) at Leeds was £21.

Antibiotic medication use in presurgical patients de-labelled before surgery

A total of 26 patients were de-labelled before their surgery across the three study sites. Sixteen of these patients were listed for procedures where prophylactic antibiotics were recommended. Of these, eight patients had a prophylactic antibiotic recommendation that differed by PAL status. The mean difference between the cost of antibiotic therapy recommended for their operations with and without PAL according to the local hospital guideline was −£2.06 (*Table 23*). No other costs incurred during follow-up were measured for these patients, for example, the cost of any postoperative wound infections.

TABLE 22 Staff costs of SPACE intervention at Leeds site (£)

	Total cost at each step (a)	Number of patients undergoing each step (b)	Cost per patient at each step (a/b)	Total cumulative costs at each step (c)	Total cumulative cost per patient at each step (c/b)	Total cumulative costs per screened patient (d)
Screening/ identification	7947	990	8	7963	8	8
Consent	4521	205	22	12,483	61	13
Risk stratification[a]	4739	89	53	17,222	194	17
Direct oral challenge	3144	32	98	20,366	636	21
De-labelling and follow-up	698	31	23	21,064	679	21

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TABLE 23 Costs of antibiotic medication use in presurgical patients de-labelled before surgery (£)

Study site	Specialty	Number of patients	Antibiotic cost (no PAL)	Antibiotic cost (PAL)	Cost difference
Birmingham	Gastrointestinal	1	0.84	1.69	−0.85
Birmingham	Urology	1	2.16	10.59	−8.43
Birmingham	[ENT (*n* = 2)], bariatric surgery (*n* = 2), urology	5	0.00	0.00	0.00
Leeds	Gynaecology	1	2.92	2.92	0.00
Leeds	Colorectal/gastrointestinal	4	1.27	9.05	−7.78
Leeds	Urology	3	1.21	1.21	0.00
Leeds	Breast	1	0.84	14.58	−13.74
Leeds	General	4	0.00	1.29	−1.29
Oxford	ENT	1	1.79	1.81	−0.02
Oxford	Urology	1	1.81	3.85	−2.04
Oxford	Maxillofacial, Interventional Radiology, ENT	3	3.85	0.00	3.85
Oxford	Maxillofacial surgery	1	0.84	1.69	−0.85
Total	Weighted mean	26			−£2.06

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Antibiotic medication use in therapeutically delabelled patients (acute medical/infectious diseases unit)

Table 24 presents the costs of the penicillin regimen in each of the six 'therapeutically de-labelled' patents in the study. It shows a cost comparison analysis following switching to a penicillin antibiotic versus a scenario of receiving a non-penicillin antibiotic if they were not de-labelled. Costs are calculated for the 5-day post DPC follow-up.

TABLE 24 Costs of antibiotic medication use in AMU/IDU therapeutic de-labelled patients (£)

Patient	Actual route after de-labelling	Cost of antibiotics after PAL removed (a)	Alternative antibiotic route (if patient had retained PAL)	Cost of alternative antibiotics (if patient had retained PAL) (b)	Cost difference (a–b)
1	Amoxicillin 500 mg PO three times a day	0.50	Doxycycline 200 mg, once daily PO, for 1 day, then 100 mg PO once daily for 4 days	0.23	0.27
2	Amoxicillin 500 mg PO three times a day	0.50	Doxycycline 200 mg PO once daily for 1 day, then 100 mg PO once daily for 4 days	0.23	0.27
3	Amoxicillin 250 mg twice daily for 1 day PO, then piperacillin/tazobactam 4.5 g IV two times a day for 4 days	12.79	Ciprofloxacin 400 mg IV twice daily	25.45	−12.66
4	Amoxicillin 1 g three times a day PO	1.00	Ciprofloxacin 500 mg PO twice daily	0.55	0.45
5	Co-amoxiclav 1.2 g IV three times a day for 3 days, then piperacillin/tazobactam 4.5 g IV twice a day for 2 days	11.41	Ceftriaxone 2 g IV once daily and clarithromycin 500 mg PO twice daily	7.74	3.67
6	Piperacillin/tazobactam 4.5 g IV three times a day	23.93	Ceftazidime 2 g IV three times a day	24.90	−0.975
Mean		8.20		9.85	−1.49

IV, intravenous; PO, oral.

Note
Duration costed is 5 days. Medication costs are from eMIT National Database.
There are *N* = 6 therapeutically de-labelled patients in this analysis. One patient was switched from opportunistic de-labelling to therapeutic de-labelling at Birmingham site (patient UH1010 described in *Table 10*). This accounts for the discrepancy between the total number of therapeutically de-labelled patients in AMU/IDU presented in this table (*n* = 6) and the corresponding figure in *Chapter 2*, *Table 8* (*n* = 7). Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

In the study, six patients were therapeutically de-labelled in AMU. Where PAL was removed, the average antibiotic cost was £1.49 less than if they had retained the PAL. This was driven by one patient with expected savings of £13.

Summary of costs

Cost savings in antibiotic use and LOS among the 26 patients from the presurgical group who underwent DPC before their surgery and the 6 patients therapeutically de-labelled in AMU/IDU were negligible compared to the intervention costs of £51 per screened patient with a PAL. The same applied to antibiotic use in primary care over 12 months after DPC, and episodes of NS among haematology-oncology patients over a chemotherapy course after DPC (see *Report Supplementary Material 3*).

Sensitivity analysis

Figure 9 illustrates the effect of the proportion of patients approached among all those identified as eligible on the cost per de-labelled patient. As more patients are approached for participation, the technical efficiency of DPC increases (i.e. cost per de-labelled participant diminishes), as the cost of screening 'missed' eligible patients becomes smaller in absolute terms and is divided up between more de-labelled patients. *Figure 9* also reveals that there is greater scope for economies of scale in Leeds by increasing its coverage rate from the 46% of eligible patients that were approached in the study than increasing coverage in Birmingham or Oxford, from their respective observed rates of 69% and 78%. These estimates are based on the results of the probabilistic sensitivity analysis. For example, a 10% increase in

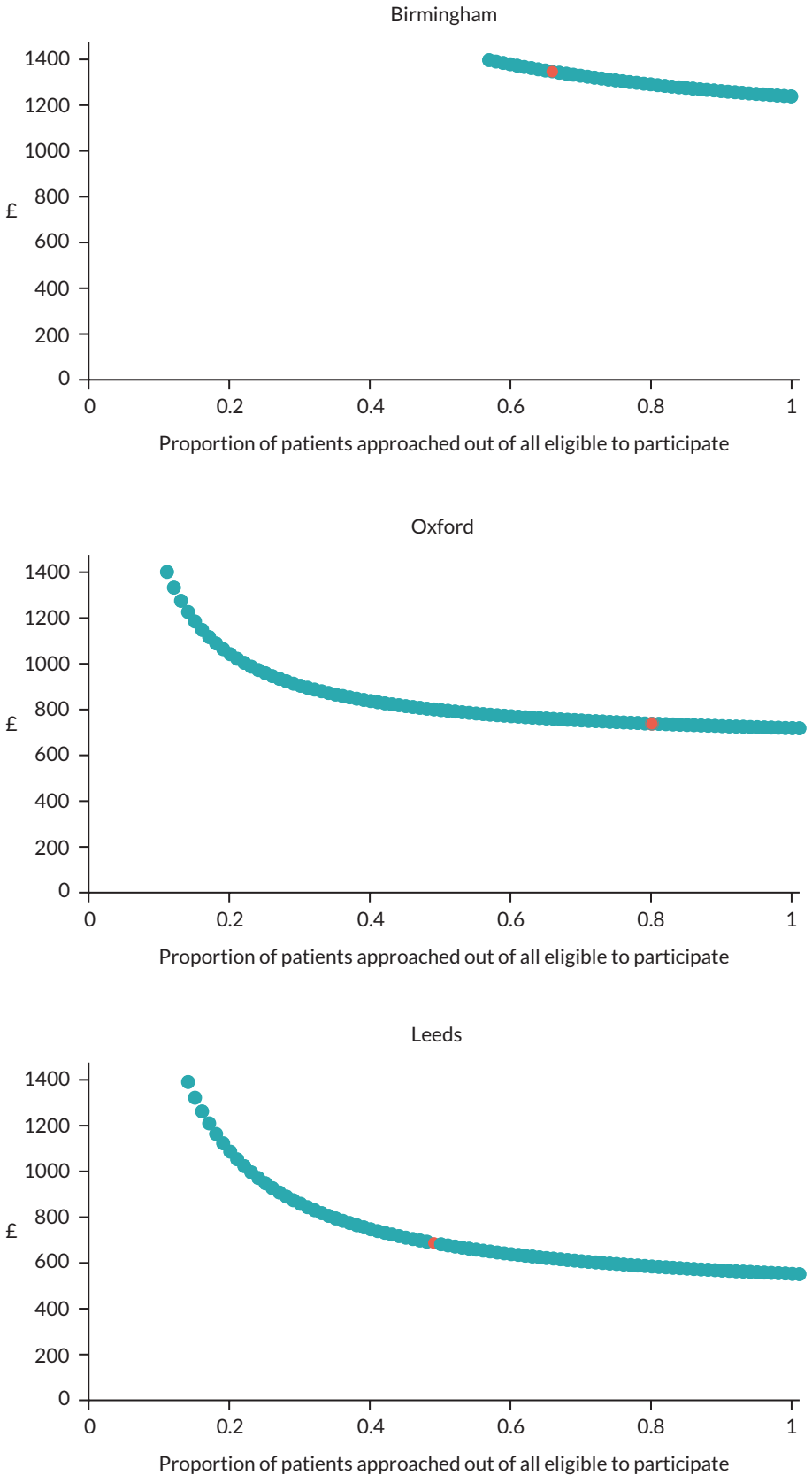

FIGURE 9 Cost per de-labelled patient as a function of conversion rate at each study site. Reproduced with permission from Bestwick *et al.*[70] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, 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.

coverage rate (from 46% to 51%) at Leeds would reduce the cost per de-labelled patient by 3.8% (from £695 to £669), while at Birmingham (69–76%) it would do so by 2.1% (£1322–1304) and at Oxford (from 78% to 86%) by 1.2% (from £722 to £714).

Small variation in costs resulted from exploring alternative staff skill mix scenarios for Birmingham and Oxford. If Grade 7 nurses performed screening and consent at Oxford, instead of these tasks being performed by RPs as occurred during the SPACE study the staff costs per de-labelled patient would reduce by 3% (from £722 to £699). At Birmingham, optimisation of the DPC model by Grade 5 RNs undertaking the screening instead of these activities being performed by the Senior RP as in the SPACE study, reduced the costs per de-labelled patient by 8% (from £1344 to £1240).

When we omit the costs of screening and day 5 follow-up, effectively assuming these activities will become embedded in the current practice so that no opportunity costs would be incurred for them, the cost per de-labelled patient will fall by 26%, 16% and 39% in Birmingham, Oxford and Leeds, respectively (*Table 25*). In contrast, if we include the annual costs of training, effectively assuming that these costs would need to be incurred every 2 years, the staff cost per de-labelled patient would increase by 13%, 10% and 17%, respectively.

Subgroup analysis

According to our exploratory analysis, in most patient groups across the study sites the observed costs of DPC per de-labelled patient are expected to be larger than the modelled cost savings, which include reduced LOS in initial admission and reduced 90-day re-admissions (for 33% of AMU/IDU patients therapeutically de-labelled and 9% of presurgical ones de-labelled before surgery, requiring antibiotic prophylaxis and not yet on penicillin, as observed in the SPACE study), reduced LOS of 90-day re-admissions and reduced GP contacts and associated costs of prescriptions up to 4.5 years after DPC (*Table 26*). The difference in the costs of DPC and cost savings (total net costs) per patient range from −£108 for haematology-oncology patients in Leeds to £1663 for AMU/IDU in Leeds. AMU/IDU was also the costliest patient group at Birmingham at £1163. The net total cost per de-labelled patient in the pre-surgical group was lowest in Leeds at −49 (95% CrI: −350 to 43), followed by Oxford at £89 (−145 to 222) and Birmingham at £655 (346 to 997).

Value of information analysis

The value of conducting further research would be mostly driven by measuring the costs of general practitioner visits over a 4.5-year period. For the average patient over such a follow-up period, avoiding the extra 13 general practitioner visits expected per patient with a PAL relative to patients without a PAL would amount to a present discounted (at an annual 3.5% rate) value of cost savings of £603 (including prescription costs), as opposed to £45 savings from 90-day hospital re-admissions (including the reduction in LOS).

To illustrate the maximum value, that is, the EVPI of conducting further research in DPC to measure these medium-term outcomes, we take the case of presurgical patients using costs experienced at the Leeds study site. The per-patient EVPI is estimated to be £5.83 per patient, which, multiplied by the expected number of de-labelled cases (at the 97% de-labelling rate) among low-risk presurgical patients eligible to undergo DPC in 1 year at 213 UK NHS hospitals (*N* = 83,670; Savic *et al.*[78]), amount to £488,165. Extending the number of years would proportionally increase the value of research to establish the impact of DPC on 90-day hospital re-admissions, LOS at the initial admission and 90-day re-admissions and general practitioner attendances over the first 5 years.

The greatest value of future research would be expected to be derived in investigating the Leeds model in haematology-oncology patients. Overall, however, researching the Oxford model presents the greater value of the three models, with little difference between which of the three patient groups is the focus of future study (*Table 27*). While further research into the Leeds model may be justified, new evidence would likely influence a policy decision to adopt DPC – if that hinges on whether the new service pays for itself – the most in relation to the Oxford pharmacist-led model.

TABLE 25 Sensitivity analysis: staff costs per de-labelled patient (£)

	Birmingham	Oxford	Leeds
Base case	1344	722	679
With training costs[a]	1516	795	796
Without screening costs	1026	626	423
Without screening and day 5 follow-up	1001	607	414

a Training costs were included as the equivalent annual flow of user capital cost, assuming the amount of investment in training at each study site has a 'productive life' of 2 years, discounted at an annual rate of 5% for the second year. Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

TABLE 26 Patient subgroup analysis by study site in £ (95% CrI)

	AMU/IDU	Presurgical patients	Haematology-oncology
Change in LOS initial spell[a,b,c]	−18	−5	0
Change in 90-day re-admissions[d]	−39	−11	0
Change in LOS of 90-day re-admissions[c]	−7	−7	−7
Change in GP contacts at 4.5 years (discounted)[e]	−287	−287	−287
Change in GP prescription costs at 4.5 years (discounted)[e]	−316	−316	−316
Total (A)	−667	−626	−610
Birmingham			
DPC per de-labelled patient (B)	1829 (1115 to 4943)	1280 (1027 to 1608)	1483 (1085 to 2206)
Net total costs (B–A)	1163 (426 to 4262)	655 (346 to 997)	874 (442 to 1558)
Oxford			
DPC per de-labelled patient (C)	747 (627 to 1041)	715 (582 to 811)	707 (520 to 1207)
Net total costs (C–A)	81 (−129 to 390)	89 (−145 to 222)	98 (−149 to 619)
Leeds			
DPC per de-labelled patient (D)	2329 (947 to 19,504)	577 (370 to 633)	502 (269 to 1438)
Net total costs (D–A)	1663 (262 to 18,832)	−49 (−232 to 179)	−108 (−405 to 823)

a By presurgical patients de-labelled before surgery.
b For therapeutically de-labelled patients.
c Based on estimated LOS differences between spells of adult patients admitted to a medium-sized hospital in Truro over a 2-year period with and without a penicillin allergy record for whom an antibiotic was used (Powell *et al.*[19]).
d Based on the 4- to 12-week readmission rate ratio reported in the study by Van Dijk et al. to convert the ONS readmission rates to 90 days.[79]
e Based on a retrospective cohort study of primary care patients with a penicillin allergy record in the Utrecht area, the Netherlands, matched for age, gender, follow-up period with three patients without a PAL and followed up over 4.5 years; figures are discounted at annual rate of 3.5%.[75] Reproduced with permission from Bestwick *et al.*[70] 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 table includes minor additions and formatting changes to the original text.

TABLE 27 Expected value of perfect information: modelled 5-year time horizon after DPC

Parameter	Expected value of perfect partial information per patient (£)		
	Birmingham model	Oxford model	Leeds model
AMU/IDU	0	24.09	0.08
Presurgical	0	25.31	5.83 2.96
Haematology-oncology	0	22.27	108.10

Discussion with local managers

Separate meetings were held with one or two local managers at each study site to identify the evidence that would be useful for planning future adoption of DPC. These involved the operations manager for HIV Allergy and Immunology and IDU and the general manager for lower general surgery at Birmingham Hospital Trust; the clinical unit manager of the clinical immunology department at Oxford University Hospitals Foundation Trust; the Head of Nursing, Theatres and Anaesthesia at Leeds. At these meetings, the clinical PIs and pharmacists and nurses driving the intervention were also present and participated in the discussions.

The meetings started by presenting the objectives of the meeting and summarising the emerging evidence on the magnitude of cost savings from DPC. Then the discussion centred on three questions. Firstly, the managers were asked about the type of evidence that would be needed to convince them that adopting DPC was a worthwhile use of the existing human and material resources under their purview. Second, they were asked about what special arrangements would be needed in addition to existing current practice at their trust to be able to provide the service. Third, we sought to find out about the practical or logistical areas of uncertainty that would need to be addressed by further research and subsequent agreement between stakeholders before the new service could be adopted.

With regard to the first question, it emerged that in addition to evidence on the health-related quality-of-life benefits to patients of removing an incorrect PAL in terms of reduced use of broad-spectrum antibiotics accruing to patients who need penicillin, evidence on the financial impact to providers and cost savings associated with reduction in hospital bed-days would be needed to strengthen the economic case to managers. In particular, establishing a link between the adoption of DPC and its consequences for relieving pressures on existing bed capacity through reduced hospital admissions and referrals to allergy services would be most useful for resource planning at the Trusts. It was also suggested that evidence of the impact on service reorganisation of managing patients remotely through an outpatient DPC service model would be relevant.

The question on required arrangements for providing the service was motivated by the study hypothesis that DPC could be provided within existing human and material resources available at the study Trusts. While there was agreement that the experience in the study pointed to the difficulty of delivering DPC within the highly pressurised context of therapeutic de-labelling of AMU/IDU patients, the results of the study suggested opportunistic DPC would be practical within the existing organisation of services. In particular, clinical lead study investigators thought there was a learning curve in the initial months of the study beyond which the demands placed on allergy specialists supervising DPC would diminish as pharmacists and nurses gained experience delivering the service. It was also thought that at Leeds there had been less opportunity for nurses delivering DPC to have sufficient number of patients tested to benefit from such learning curve within the limited duration of the study.

The preceding considerations brought the focus on to the small proportion of patients whose DPC was performed before surgery and on ways to optimise surgical prophylaxis. In this regard, the managers and clinical leads identified

the need for an additional health professional staff role with basic training required to identify eligible patients at the time of the preoperative outpatient assessment visit using a simple checklist and triage them to the fully trained nurse/pharmacist to conduct the risk stratification and DPC.

Three remaining areas of uncertainty were perceived by the managers as to how services would be organised. First, they pointed to the need to ascertain whether the service would be adopted in an inpatient setting only and managed by the allergy service or whether it would also accept patients on an outpatient basis, possibly referred externally from other hospitals or teams within the trust. The second uncertain area was about governance and the professional who would have clinical responsibility for the patient receiving the service. In particular, from the point of view of the consultant, it would need to be determined whether that responsibility would be assigned on a rotational basis. If alternatively, the service was meant to be added as a 'bolt-on' to current services, a designated consultant in charge of DPC might need to be employed and, if so, additional funding allocated following a business case, given the current strain on the allergy team and lack of capacity to open extra clinics for a new service. In Birmingham, DPC provided as an inpatient-only service would need to be channelled through acute services in coordination with allergy services, through a new alert and coding system to identify and refer patients (there is no ward specific for allergy as patients walk in through the front door who need to be admitted to a medical ward under medicine as a whole).

Discussion

As the SPACE study was not designed to collect patient outcomes, we could not evaluate the cost-effectiveness of DPC. Instead, we have conducted a detailed cost analysis of delivering a non-allergy specialist-led DPC in a hospital setting across three different models of service delivery for three different specialties, with opportunistic or therapeutic de-labelling aims. The study sought to infer antibiotic cost savings that may occur immediately after DPC in therapeutically de-labelled patients in AMU/IDU (N = 6) and patients on the presurgical list who were de-labelled before surgery (N = 26). Given its uncontrolled short-time follow-up, the revised target number of 126 DPCs, and the heterogeneous patient group, this study was not designed or powered to capture the high-cost negative outcomes associated with the unnecessary use of broad-spectrum antibiotics among patients with an incorrect PAL. Similarly, capturing most of the cost savings that are likely to occur after de-labelling and over the remaining patient lifetime was beyond the scope of the study. We nevertheless conducted an early economic evaluation of conducting a future longitudinal research study that seeks to measure cost savings up to 5 years after DPC, while identifying the key outcomes to measure in such a study and the minimum rate of conversion required for DPC to be cost saving to the NHS.

We found that performing DPCs in AMU/IDU patients was more costly than DPCs in other patient groups. This is more starkly illustrated in Leeds, where the cost per de-labelled AMU/IDU participant was 12 times that for de-labelling presurgical participants. This magnitude reflects the lower conversion rate achieved among AMU/IDU patients, which in the case of Leeds led to stopping screening in this patient group after the first 3 months of recruitment and reallocating the efforts to identify patients from the other two patient groups instead.

In terms of the costs of the different models, we found that the model based on RNs, as practiced in Leeds, resulted in lower costs than the pharmacist-led model in Oxford and the mixed pharmacist and nurse model of Birmingham. Further unlike Oxford, Birmingham site had an admin or data manager to support the delivery of DPC. Our analysis showed that while the service in Oxford and Birmingham achieved close to optimal levels of technical efficiency at high coverage rates, DPC in Leeds had potential to increase its 50% coverage rate of eligible patients to exploit economies of scale. Whether economies of scale do materialise as DPC is being offered to more eligible patients will depend on whether our implicit assumption of constant marginal costs of increasing nurse capacity is confirmed in a future, larger study.

Besides the cost of delivering DPC, a key aspect likely to facilitate adoption is its cost-effectiveness. Although the study did not set to answer this question, we explored the potential of DPC to generate cost savings. Previous studies have found that DPC in an inpatient setting is capable of producing enough savings to pay for itself. Brusco *et al.*[80] found that an oral challenge in Australia costs £23 and was associated with cost savings in low-risk patients of £4511 (at 2022 purchasing power rates) in acute patients, to which antibiotics and intravenous consumables contributed only £8 and

£34 and the rest was associated with reduced LOS. In the minority (6 out of 126) of our therapeutically de-labelled study participants the antibiotic cost saving per participant was expected to amount to only £1, while the oral challenge step cost between £90 and £288 depending on the centre. Moreover, results from a recent study in a medium size hospital suggest savings from removing a PAL would be expected to amount to £50 per de-labelled patient.[37]

Two more studies evaluated the DPC in an inpatient setting, of which only one evaluated the cost of the intervention. Ramsey *et al.* reported the cost of a 3-day amoxicillin DPC by an allergist that includes the cost of amoxicillin, pharmacist preparation time and the consultation of £137, which was partly offset by direct antibiotic cost savings of £120.[81] The other study was a case series of 70 patients retrospectively matched to controls that did not measure the cost of DPC and reported large antibiotic cost savings of £170 for a combined savings from antibiotics and LOS of £3260 and a reduction in the number of 6-month re-admissions of 0.18 (0.61 controls vs. 0.43 oral challenge).[82] The study suggests that these studies may be presenting an incomplete picture of the costs associated with delivering DPC in an inpatient setting since they omit the costs of activities required to identify and risk stratify patients before they can be given the DPC, which in the study added £540–1000 per de-labelled patient on top of the costs of the oral challenge step.

Discussions with local managers highlighted that extra nursing staff may need to be employed in optimising the number of patients with PAL requiring presurgical penicillin prophylaxis who are identified sufficiently early to be able to benefit from DPC at the Leeds study site. Previous studies suggested that, by avoiding revisions due to prosthetic joint infections, removing a PAL would save more in healthcare costs than the cost to providers of the service in the first place among patients undergoing hip and knee replacement.[83] Although a longitudinal evaluation of benefits among presurgical patients was beyond the scope of the study, our modelling and value of information analysis of European evidence on resource use differences between patients with and without PAL found that measuring outcomes of repeat general practitioner visits in future studies may prove as, if not more, important for evidencing cost-effectiveness of DPC as its impact on hospitalisations. This may be partly supported by observational findings from a US study that retrospectively matched 308 penicillin allergy-tested patients to 1251 non-tested penicillin allergy controls and found that, over a 3.6-year follow-up, the former had 0.09 fewer outpatient visits, 0.13 fewer emergency department visits and 0.55 fewer hospital days per year.[84]

Overall, our value of information analysis found that the most valuable future research would be to investigate whether DPC under the Leeds model produces enough cost savings in haematology-oncology patients to be attractive to health service providers and the NHS. Across patient groups, the model where research would shed most light is the pharmacist-led model at Oxford, and the three patient subgroups investigated in the SPACE study would be almost equally fruitful targets of research efforts and resources.

DPC has a role in increasing access to patients with a PAL who currently do not have any route to proactively seek allergy testing in the NHS. Currently, penicillin allergy testing is only available through skin tests provided by outpatient allergy specialist clinics by GP referral, and lack of capacity means few patients get referred to these services. Moreover, previous studies have shown that skin tests are twice as costly as DPC.[81]

Future research should seek to capture outcomes that were beyond the scope of the study, including the impact of DPC on the risk of healthcare-associated infections, for example, MRSA, *C. difficile*, vancomycin-resistant *Enterococcus* infection, delays in the treatment of sepsis and meningitis, mortality in patients presenting with pneumonia and a PAL, risk of perioperative anaphylaxis due to the use of teicoplanin in patients with a PAL, risk of surgical site infections postoperatively and the management of sepsis at the front door. A retrospective cohort analysis in Scotland found that *C. difficile* was associated with a median additional cost of index inpatient stay of £1713.[85]

An important limitation of our economic analysis is that the recorded healthcare resource use involved in delivering DPC was driven by the study protocol and may therefore overestimate the costs that would be expected to occur in routine clinical practice. In particular, several tasks involved in identifying and screening patients who may benefit from DPC conducted by experienced pharmacists in Oxford and Birmingham could have been performed by relatively less experienced clinical and nonclinical staff, and some tasks may also become standardised and streamlined via adoption of computerised decision support systems as DPC is adopted into routine practice, thereby reducing costs.

Chapter 5 Conclusions and future directions

Summary of principal findings

Background

The primary aims of this study were to explore the behaviour, attitudes and acceptability of patients, HCPs and managers regarding the use of DPC in 'low risk' patients and to develop treatment pathways and a governance framework for this service model.

The secondary aims were to explore the practical aspects of implementing a de-labelling programme in secondary care by investigating factors such as organisational context, treatment pathway, protocol, implementation, time taken and resources and to evaluate the potential cost-effectiveness of this service model.

Six per cent of the general population in England[4] and 15–20% of inpatients[2,3] carry a PAL. However, 90–95% of these labels are shown to be incorrect following comprehensive allergy testing.[1,5,7,9,34] Penicillins are the first-line antibiotic choice for many infections and are the most commonly prescribed antibiotics. PALs are a major barrier to AMS. The applicants and others have previously reported higher rates of AMR and serious hospital infections in patients with documented PALs in two UK population-based studies.[4,13,15]

The assessment process for PAL currently involves a systematic clinical history, a review of previous records, skin testing and a supervised oral penicillin challenge (if skin testing is negative).[20] Oral penicillin challenge is the definitive method to exclude an allergy and confirm tolerance.[20] However, penicillin allergy testing is labour intensive, time-consuming, and requires a specialist in allergy.[20] Given the burden of PALs and the huge unmet demand for allergy services, penicillin allergy tests are not routinely available to inpatients.[21,86,87] Most hospitals in the NHS do not have specialist allergy services.[87] As per national guidelines, testing is available electively only to patients at a high risk of infections or to those with a label of 'multiple antibiotic allergy' via a small number of allergy clinics.[20,88]

Our preliminary work and recent evidence from the USA, Australia and New Zealand have shown that multidisciplinary penicillin allergy de-labelling pathways employing a risk stratification process including a DPC without prior skin testing, is a promising approach to improve AMS and reduce healthcare costs.[8,52,55]

Workstreams 1–3

This feasibility study has provided further knowledge to contribute to the following areas:

1. the behaviour and perceptions of patients and HCPs in secondary care regarding the risk stratification process and DPC
2. the time and resources required to support this process and
3. the views of senior management in secondary care.

This knowledge is required to define the treatment pathways and governance frameworks to inform potential strategies for the strategic roll-out of DPC in the NHS secondary care. If this service model can be embedded into routine clinical care, this will facilitate the delivery of improved AMS and potentially provide a cost saving for the NHS.

Three WSs were undertaken to establish the feasibility of the proposed de-labelling intervention. Quantitative and qualitative data collection methods have been used to identify the individual and organisational factors and processes influencing implementation of the approach to de-labelling.

In WS1, patients were stratified into 'low risk' and high risk' by a RN and RP trained to deliver the study protocol. This was ratified by the study consultant (non-allergy specialist). 'Low risk' patients were offered an opportunity to undergo DPC.

In WS2, as the evidence base for patient and HCP perspective is underdeveloped, we adopted an exploratory approach, drawing on two qualitative research methods semistructured one-to-one interviews and focus groups at each site.[89,90] Our target population for the focus groups comprised the key stakeholders including prescribers, relevant HCPs, clinical leaders, operational managers and commissioners involved in the service changes required for adoption of the new pathway.

In WS3, care pathway mapping for penicillin allergy at the study sites and decision-analytic modelling was carried out to determine the potential cost-effectiveness of DPC.

To evaluate this, detailed analysis has been undertaken to report descriptive data on risk stratification and the uptake and safety of DPC. Transcribing and analysis of patient interviews and focus group sessions using thematic coding mapped to the theoretical domain's framework were carried out to understand the behaviour of patients, HCPs and managers towards PAL. A comparison of potential cost-effectiveness of the proposed penicillin de-labelling with current practice was undertaken.

This work was carried out to understand the issues/barriers to roll-out of this service for both therapeutic and opportunistic de-labelling in different secondary care clinical settings. These are patients admitted under AMU/IDU wards, haematology-oncology patients and patients on a perioperative pathway. A key area addressed is how to deliver DPC so that perioperative patients who are deemed low-risk can benefit from first-line penicillin surgical prophylaxis. For therapeutic de-labelling in an acute medical setting, the advantages of doing so and enabling first-line penicillin treatment in patients with serious infections such as bacterial endocarditis or bacterial meningitis are self-evident though it would be important to study its impact across a wider population.

The ensuing paragraphs, which focus on the discussion of the principal findings across all three workstreams, have been formulated to comply with the recommendations of the GRIPP2 reporting checklist on reporting patient and public involvement in research.[45]

Principal findings

Workstream 1: Results of direct oral penicillin challenge

The findings of this study add to the growing body of evidence attesting to the safety and efficacy of a DPC without prior skin testing in low-risk patients with a PAL.[9,24,34]

In order to simplify the DPC process and thus enable future systematic adoption across the NHS and other healthcare systems, a single dose of amoxicillin 500 mg was chosen in contrast to a graded approach used by other investigators.[51] The use of a single dose of amoxicillin, by virtue of its core beta-lactam ring and side chain characteristics, has equal validity for de-labelling as using a graded approach. Of note, the personnel undertaking risk stratification and DPCs had no previous background in allergy and immunology.

Our initial aim was to conduct 125 DPCs at each of the three participating sites (total of 375) but this was modified due to COVID-19 pandemic constraints to 41 per site (total of 122). The reduced number compares favourably with sample sizes in other prospective studies[34,49,50,52] and was based on revised statistical sample size calculations and received regulatory approval in September 2022.

Of the total number of 2257 patients screened with PAL on their electronic patient records, it is noteworthy that only 270 (12% conversion rate) consented to participate. Two hundred and fifty-nine out of 270 (89%) underwent risk stratification, of whom 155 (60%) were deemed to be low-risk patients and 104 (40%) high risk across all 3 sites. There were differences in conversion rates (screening > consent) between the three participating sites. Regression analysis showed progression in the study pathway and consenting to participate was significantly more likely from Oxford (OR −1.73; $p = 0.002$). It is worth exploring whether the differences in conversion rate reflected the backgrounds of triaging personnel, with prescribing pharmacists doing so in Oxford and Birmingham while non-prescribing nurses did so in Leeds. Across all three sites, patients from haematology-oncology and presurgical settings were more likely to be eligible

in comparison to patients on AMU/IDU. This is likely to reflect the inherent challenges involved in recruiting from a group of acutely unwell, frequently elderly patients with multiple comorbidities and cognitive impairment as would be typical on an AMU. Additional reasons for the relatively low conversion rate include pandemic-related restrictions in hospital attendance and the use of higher clinical thresholds in judgement for categorisation as low risk. In contrast to other de-labelling studies, the explicit exclusion of clinically unstable patients who would otherwise have been deemed to be 'low risk' is also likely to have been a contributing factor.

Of the 126 patients who finally underwent DPC, 122 (96.8%) were successfully de-labelled. This high rate of de-labelling is concordant with the results of DPC reported in the literature.[34] Two major systematic reviews of DPC carried out in both inpatient and outpatient settings have reported 94.4–96.5% de-labelling rates.[9,34] In addition, the safety of DPCs in the SPACE study taken together with the reported lack of serious type-I and type-IV HSRs in the systematic reviews, underlines the overall safety of this approach.

While the proportion of patients experiencing AEs was 19% (25 of 126; 2 SAEs unrelated to DPC), it is important to note that these were invariably mild and self-limiting, with no patients experiencing a serious type-I or type-IV HSR. This rate of AEs exceeds the rate reported in the literature of 3.4% as the mean incidence in a pooled analysis of 13 studies[34] but should not be regarded as an impediment to non-allergy HCPs undertaking de-labelling. Given the demonstrable safety of this approach, for patients with a clear history of non-immune-mediated symptoms, an alternative approach would be to consider direct de-labelling by undertaking a review of the clinical history alone without undertaking a DPC, as successfully demonstrated elsewhere.[52]

Qualitative aspects: exploration of behaviours, attitudes and acceptability of patients and healthcare practitioners of oral drug provocation challenges in low-risk patients

Qualitative aspects of the SPACE study were investigated by undertaking interviews with patients, HCPs and managers. It was evident from patient interviews across all three sites that patients had very little knowledge of the implications of a PAL and consequently tended to accept the label at face value. However, on receiving an explanation of the basis for suspecting spurious allergy, most patients appreciated the individual and wider public health benefits of undergoing a DPC for definitive de-labelling. At a practical level, the majority of patients had no major concerns regarding undergoing DPC in a hospital under close clinical supervision, but some expressed anxiety about potential reactions at the time of DPC. All participants who underwent DPC were generally positive in their description of it and would recommend a DPC, if deemed medically appropriate, to other patients with a PAL.

Focus groups with HCPs highlighted broad support for DPC while emphasising the importance of doing so within a clear organisational governance framework and support from specialist clinicians and champions. The perspectives of HCPs with regard to assessing an allergy history, risk stratification and DPC were influenced by baseline knowledge and clinical professional backgrounds. Provision of a clear allergy history-taking framework coupled with support from senior clinicians was instrumental in enabling RPs and RNs to develop confidence to undertake risk-stratification and DPC. This observation highlights the importance of improving allergy education for HCPs, which is demonstrably suboptimal in the UK undergraduate medical curriculum, with < 10% of students having an opportunity to take an independent history.[11] Although there was some site-specific ambiguity and uncertainty around the need for allergy specialist involvement, overall patients and HCPs noted a smooth de-labelling process, thus highlighting the success of a de-labelling pathway delivered by non-allergy specialists.

Economic evaluation of de-labelling: potential cost-effectiveness considerations

It is important to acknowledge that the SPACE study was not adequately powered to demonstrate formal cost-effectiveness calculations, but nonetheless aimed to assess the potential cost-effectiveness of undertaking penicillin allergy de-labelling. The changes in antibiotic use and their attendant costs as a consequence of removal of a PAL allowing the use of penicillin-based antibiotics versus not doing so were modelled for the respective clinical settings across AMU/IDU, presurgical and haematology-oncology units.

In addition to considering antibiotic costs, this modelling also incorporated the costs of the intervention for staff training and support from consultants. Using this approach, each completed DPC costs £98–162 between study sites as compared with initial screening costs of £21–76. For individual patients in presurgical settings across all sites (n = 16),

the value of de-labelling was shown as a modest reduction in costs with the use of a penicillin-based antibiotic (mean saving of £1.74). While these savings in the 8 of 26 patients who were prescribed a penicillin-based antibiotic following de-labelling was modest, the wider benefit of thus avoiding teicoplanin, a glycopeptide antibiotic well documented for causing perioperative anaphylaxis is likely to be considerable in terms of the reduction in morbidity, avoidance of critical care, abandoned surgery and potential mortality. It is worth reflecting that teicoplanin was identified as the trigger for anaphylaxis in 13.5% of patients (total 266) in the UK's sixth National Audit Project on perioperative anaphylaxis.[91] At a national level, these benefits are brought into sharp focus when one considers the prevalence of self-reported penicillin allergy in a cross-sectional survey of patients awaiting elective surgery. Of 21,219 patients surveyed at 213 NHS Trusts, 27% of patients with self-reported penicillin allergy were deemed suitable for a DPC.[78]

For haematology-oncology patients (n = 45), analysis of antibiotic costs was based on a hypothetical model of the treatment of NS in patients with and without a PAL. Based on modelling of antibiotic costs for the management of NS, mean savings were calculated at £133.37 following the removal of a PAL. As with actual savings on antibiotic costs in the presurgical setting, this analysis does not include the considerable savings attributable to the optimal treatment of NS in terms of reduction in morbidity and mortality. The validity of this approach is supported by multiple studies documenting reductions in the use of vancomycin and quinolone antibiotics following removal of a PAL.[8]

While the SPACE study did not involve longitudinal follow-up of individual patients who had been de-labelled, it could be reasonably argued that the qualitative benefits for an individual patient could potentially be considerable were they to develop a serious infection warranting a penicillin-based antibiotic as the preferred treatment. This is exemplified by the consequences of delayed treatment of patients with meningococcal meningitis and gas gangrene because of a PAL resulting in major morbidity.[92,93]

Additional evidence of cost savings and the impact of reducing the incidence of hospital-acquired infections in patients with a spurious PAL was provided by Macy *et al.*[15] In their retrospective matched cohort study of 51,582 patients with a label of PAL, the benefits of de-labelling in terms of use of appropriate penicillin-based antibiotics and reduction in the incidence of hospital-acquired infection was estimated at approximately $58 million US dollars.[15] In contrast to Macy *et al.* who adopted a de-labelling strategy based on prior skin testing, decision models of the effect of performing DPC (with or without prior skin testing) have also shown clear evidence of cost savings from a health service perspective in Europe and the United States in relation to hospital bed-days, outpatient visits and antibiotic costs. This ranged from $657 for inpatients and $2746 for outpatients.[74] If a de-labelling strategy was to be adopted across the UK NHS, it was acknowledged in discussions with health service managers across all three sites that similar considerations would apply.

While the SPACE study has focused on performance of a DPC as a central tenet of a de-labelling strategy, any discussion of cost-effectiveness should also consider the greater savings that are likely to accrue by de-labelling some patients on the basis of the history alone, where this is indicative of non-immune-mediated symptoms.[94]

Impact and learning: implications for practice and policy

Data from the SPACE study add to the emerging evidence base supporting the feasibility and safety of using a DPC without prior skin testing in low-risk patients. Importantly, this intervention has been delivered by RPs and RNs without a previous background in allergy or immunology. The use of a clear risk-stratification strategy is key to this, with the simplicity of this approach being an attractive proposition for its adoption across the NHS. As emphasised during interviews with HCPs and patients, it is important to have a clear governance framework to support its introduction across a major sector of secondary care, which does not have specialist allergy-immunology services. Uptake and widespread adoption of DPCs as a core part of the assessment of any inpatient with a PAL will require national leadership to articulate the benefits of de-labelling for individual patients and the wider societal benefits of reducing AMR and enhancing overall AMS.

While the literature on penicillin allergy de-labelling has highlighted the high success rate of DPCs, it has hitherto not focused on the gulf between the total number of patients with a PAL as opposed to the proportion who consent to undergo risk stratification. The SPACE study has been relatively unique in highlighting this low conversion rate at 12%. However, recently a de-labelling study in low-risk patients with COVID-19 also identified a lower conversion rate of < 10%.[53] A wider lesson from this study is the demonstration of the safety and efficacy of penicillin allergy de-labelling

in critically ill patients once they have been stabilised. A targeted multipronged approach is needed to enhance the engagement of inpatients and outpatients including those who may be deemed unsuitable at the point of initial screening, suggesting the requirement of a robust follow-up mechanism to determine an optimal time point for risk stratification and DPC (summarised in *Figure 10*).

Success in undertaking systematic de-labelling would be measured by the introduction of a DPC for all low-risk patients with a PAL across the NHS. This point was cogently stated by a patient representative who expressed a wish for de-labelling to be considered as a routine intervention ('similar to checking blood pressure') in the assessment of a patient with PAL in either primary or secondary care. This would be achievable if training for screening and risk stratification was included during the induction of junior medical staff and facilitated by the use of a point of care computerised guideline with decision support at the bedside or in outpatients, as has been successfully demonstrated in the United States and Australia.[25,95] Adoption of de-labelling as policy across the NHS will require many Trusts to consider the staffing and training requirements for successful implementation. Policy implementation would also be significantly enhanced by the designation of existing senior clinicians in key specialties to act as penicillin allergy de-labelling champions.

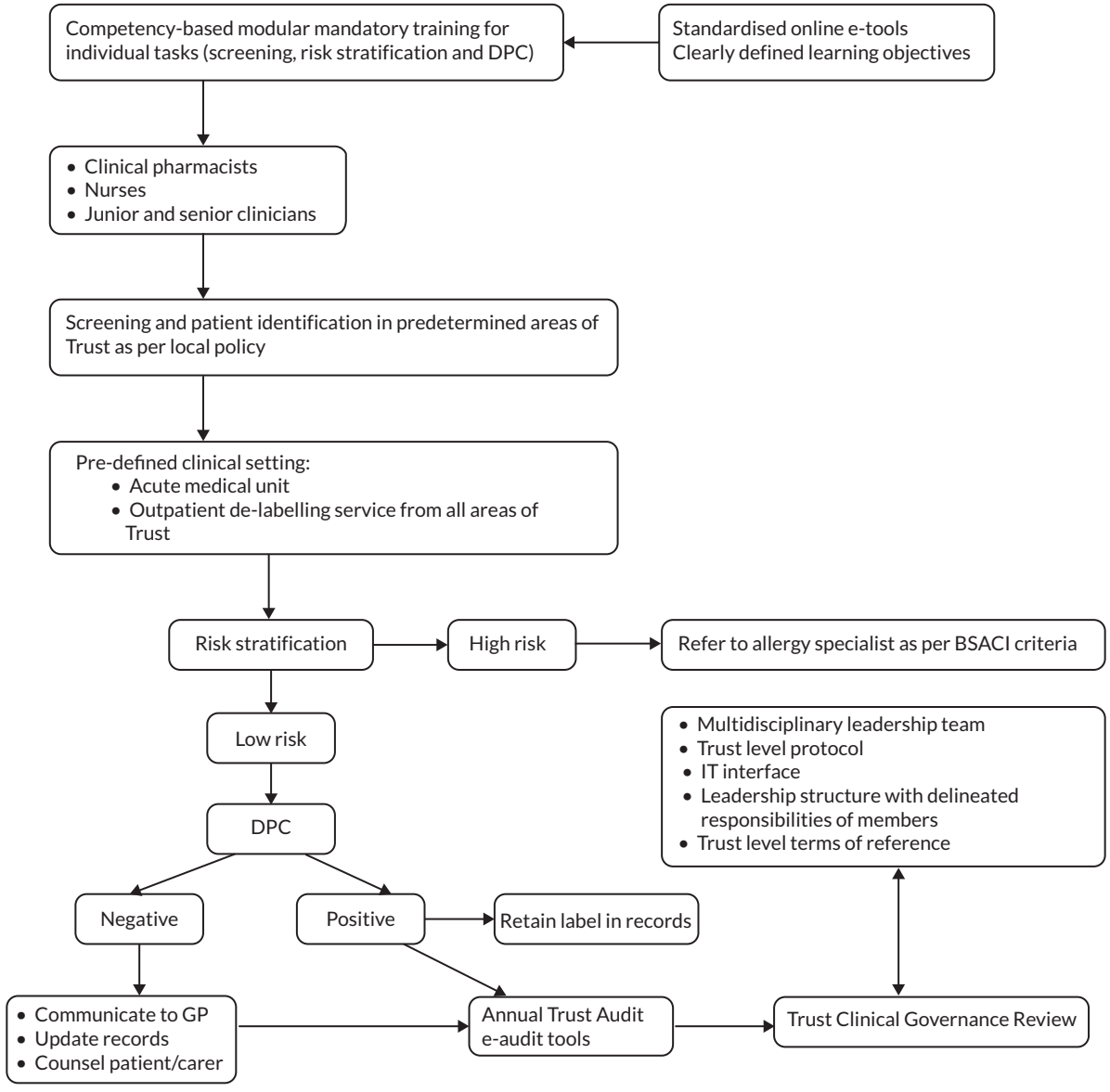

FIGURE 10 Proposed patient pathway and governance structure for non-allergy specialist-led penicillin allergy de-labelling.

Reflections of study team

Successful completion of this study amidst the COVID-19 pandemic proved to be a major logistical challenge, which was overcome by a combination of enthusiastic research staff and close co-ordination between the study teams at the respective sites in Birmingham, Oxford and Leeds. While the framework employed in the SPACE study utilised specialist allergist-immunologists at two of the three centres as principal or chief investigators, these individuals were not involved in triaging and risk stratification decisions which were made by RPs or RNs with support from study consultants without specialist expertise in allergy or immunology. This was an important point highlighted by the ability of these allied HCPs to effectively undertake risk stratification followed by DPC after receiving appropriate training. This was a major factor in successful completion of the study.

Demonstration of the simplicity and safety of this approach for both therapeutic and opportunistic de-labelling underlies the conviction of the study team that adoption of a formal de-labelling strategy using non-allergy specialist staff across the NHS is both feasible and practicable, subject to strong leadership and investment in staffing. Our findings add to the growing consensus amongst allergists and immunologists, exemplified by the recent guideline from the BSACI, that risk-stratification and de-labelling in low-risk patients can be performed by non-allergists in settings with appropriate safety standards.[40] Successful delivery of such a de-labelling programme in low-risk patients using DPC performed by pharmacists without the support of allergists has recently been demonstrated in an inpatient setting in the UK (CATALYST study – challenging antibiotic allergy status).[49] It is noteworthy that pharmacists involved in this study felt that the process of de-labelling was intuitive and self-explanatory.

Strategic implementation of direct oral penicillin challenge

The development and roll-out of a new service model for DPC would require a staged approach. We anticipate introduction of this intervention is likely to occur first in teaching hospitals with an 'in-house' allergist/immunologist. This would require active engagement with relevant stake holders related to allergy and AMS programmes including NHS England and the UK Health Security Agency. However, the simplicity and safety of the DPC also lends itself to early adoption in smaller hospitals without specialist allergists or immunologists. A 'hub and spoke' model, with a regional centre supporting smaller Trusts without an allergy specialist may be the next step in the process. For those institutions who have hitherto not had a penicillin allergy de-labelling service, launching a programme de novo is likely to represent a significant cultural change. Such a programme may also be regarded as relatively complex because of its dependence on the attitudes and behaviours of staff delivering the intervention,[96] notwithstanding the simplicity of risk stratification and the safety of DPC. These potential barriers are, however, surmountable if a penicillin allergy de-labelling service was developed with the backing of a strong governance framework.

The key elements of a clinical governance framework for delivery of penicillin allergy de-labelling are summarised as follows:

- Endorsement of strategy by Trust Leadership as a key pillar of AMS.
- Designation of clinical champions in relevant clinical areas where an incorrect label of penicillin allergy carries major adverse implications – ID, General Medicine, Haematology-Oncology, Presurgical assessment.
- Provision of clear risk-stratification algorithm using computerised decision support systems at the point of care.
- Provision of training to HCPs to undertake risk stratification.
- Designated support from senior clinicians with access to advice (if required) from specialist allergy-immunology service.

The applicants are well placed to liaise with the relevant stakeholders and patient organisations to facilitate the implementation process. The findings from the current study will aid business case preparation and decision-making, enable organisations to embed these processes into their strategic planning and governance processes, and promote inclusive approaches to business case development, thereby increasing transparency of local government and NHS resource allocation.

Successful roll-out of DPC by non-specialists across the NHS will require consideration to the following points highlighted in the SPACE study (see *Figure 10*):

- Recognition of the facilitators and barriers and the strategic planning required to aid implementation in the NHS.
- Practical steps required to move towards NHS roll-out including supportive measures for those from ethnic minority groups with suboptimal English language proficiency.
- Estimation of the uptake (81%) of DPC by 'low risk' patients to enable service planning.
- The demonstration of safety of DPCs to offer reassurance to patients, patient organisations and HCPs to enhance uptake of this intervention.
- Identification of the appropriate clinical settings for intervention. While de-labelling is clearly feasible in the three settings described in the study (AMU, presurgical and haematology-oncology), it is also possible to offer this intervention in an outpatient or ICU setting to unstable patients once they have recovered from acute illness.[53]
- Incorporation of computerised decision support systems to support de-labelling in existing IT systems, including portable electronic devices and the cascading of allergy status to primary care.
- Clinical governance frameworks including leadership and defining roles for membership of multidisciplinary teams.
- Audit tools to monitor delivery and safety.
- Involvement of patients and patient organisations in the implementation process.
- Health Economic Modelling data to help in strategic planning for hospital managers.
- Engagement of a wide range of stakeholders including the Royal College of Physicians, the Royal College of Child Health, the Royal College of Nursing, the BSACI, the British Society of Antimicrobial Chemotherapy, the Royal College of Anaesthetists, Medical School Council and the Royal Pharmaceutical Society of Great Britain to enhance the uptake of this intervention across in the UK NHS.

Study limitations

The SPACE study has a number of inherent limitations which have been acknowledged elsewhere in this report, including in the preceding paragraphs of this chapter. For ease of understanding, an overview of study limitations has been collated and provided here.

The COVID pandemic necessitated a significant reduction in sample size for DPC (from 375 to 122). Allied to this, was the unanticipated low conversion rate of 12% of patients (270 of 2257 with PAL). Neither of these points is likely to have materially influenced the validity of study outcomes given that the de-labelling rate of 96.8% accords with the results of DPC in low-risk patients as reported by others.

Understanding the perspectives of patients and HCPs in undertaking de-labelling was covered by qualitative studies comprising thematic analysis of interviews. The limitations of this approach in relation to possible biases and variations in risk perception have already been addressed in *Chapter 3*. Specifically, there were very few low-risk patients interviewed who had declined undergoing DPC, potentially introducing a positive bias towards acceptance of this intervention in the qualitative analysis.

While the SPACE study was not designed to consider longitudinal impacts of de-labelling on antibiotic use, AMS, cost-effectiveness and individual patient management these factors are nonetheless acknowledged as limitations. Furthermore, the potential impact and/or bias due to the pandemic on the patient populations in respective clinical settings (i.e. whether different to pre and post pandemic) is also acknowledged as a limitation.

Notwithstanding these limitations, the SPACE study is the only multicentre investigation of penicillin allergy de-labelling in the UK. It provides clear evidence of the ability of allied HCPs, with no previous background in allergy and immunology to safely undertake risk-stratification and successfully perform drug provocation challenge. Further evidence for the safety of amoxicillin drug provocation challenges in 1002 low-risk patients has been reported recently.[97]

When combined with increasing recognition that direct de-labelling (without drug provocation challenge) is also safe and feasible for a significant proportion of patients with PAL, this constitutes a strong argument for the adoption of penicillin allergy de-labelling across the NHS.[48]

Proposals for development of 'fit for purpose' information technology systems and cascading allergy status to primary care

Experience in the SPACE study demonstrated it is important to take advantage of the UK NHS digitalisation for success in penicillin allergy de-labelling. In the SPACE study, penicillin allergy de-labelling involved identification of people with PAL, screening for eligibility, risk stratification of the index reaction of consented participants, administration of the DPC, updating hospital allergy records, counselling the participant, and communicating the outcome of the DPC (low-risk participants) or risk stratification (high-risk participants) with the participant's GP. At an organisational level, appropriately trained staff, governance frameworks and healthcare digitalisation have been identified as components required for a penicillin allergy de-labelling service.

The utility of existing NHS digital resources for delivering penicillin allergy de-labelling was evident from the WS2 and WS3 findings. All centres in the SPACE study were able to identify patients with PALs from electronic patient records. However, screening of PALs for eligibility in the SPACE study was limited by ambiguous, incomplete, and poor-quality penicillin allergy documentation. Wanat *et al.* described similar barriers in the exploration of spurious PALs.[43]

Taking an accurate allergy history is crucial for risk stratification which can be standardised with the support of NHS digital services. The NICE guideline (CG183) can be used as a national standard for taking a comprehensive drug allergy history by non-allergy specialists in the UK.[88] The SPACE study risk stratification toolkit can be embedded into a 'fit-for-purpose' IT system which can act as a decision tool for the outcome of the risk stratification, for example, high risk or low risk. Low-risk participants can then be considered for a DPC in the UK NHS. There are similar successful digital concepts that have already been established in other countries. The PEN-FAST tool developed by Trubiano *et al.* has been validated to be used by clinicians and AMS programs to identify low-risk PAL at point of care.[25] For organisations that do not have an EP platform, the penicillin allergy de-labelling process is still possible through an application for use on mobile electronic devices.

In the SPACE study, the outcome of the penicillin allergy de-labelling was communicated by generating standardised model letters. These were sent to participants via post and post or e-mail to GPs. In future NHS Digital should focus on the development of digital healthcare systems that enable a synchronised communication of allergy information across primary/secondary care interfaces and a national governance framework on how to embed such systems into routine clinical practice in the UK NHS. Prospective labelling of 'true' penicillin reactions can also be facilitated by such systems.

In the UK NHS, the focus should be to develop national penicillin allergy dashboards to screen patients with the SPACE study eligibility criteria for risk stratification and potentially penicillin allergy de-labelling across the primary/secondary care interface. These dashboards could be used in primary care to identify patients in GP practices with a PAL and interlink with IT systems used in primary care. In addition, this dashboard should be available at a ward level in secondary care to enable an opportunity for penicillin allergy de-labelling in routine clinical practice.

Although success of digitalisation for penicillin allergy de-labelling in the UK is limited by the complexity of the IT systems in primary and secondary care, these may be overcome by national influences from NHS England, NHS digital and the national AMS strategy driving national change, national standards, and excellence in patient care.

Equality diversity and inclusion

This study was carried out at three centres (Birmingham, Oxford and Leeds). This purposive sampling of three geographically distant NHS hospitals was to capture a range of NHS clinical services and socioeconomic and ethnic diversity amongst participants. The patient population reflected those who would present to a university

and district general hospitals, and geographical spread has helped to promote diversity and inclusion amongst our research participants.

Patient inclusion criteria were defined to encourage diversity in terms of gender, age and ethnicity. These demographics were recorded to allow us to review diversity amongst the study participants. We appreciate the need to ensure that any widespread NHS roll-out of a penicillin allergy de-labelling service is accessible and acceptable to our diverse secondary care patient group. Patients interviewed included low-risk group who underwent and declined DPC, although the majority comprised the former. Interviews were offered either face-to-face or via virtual platforms or telephone to remove barriers to participation wherever possible. Targeted patient recruitment was carried out to create a diverse interview sample with respect to gender, age and ethnicity.

To promote diversity and inclusion as an underpinning principle of the study, patients and members of the public were fully involved in every aspect of this study since its inception and have advised on strategies to ensure study participant inclusion. Groups involved are the Patient and Public Involvement in Research (PPIR) team at UHB, which comprises the UHB PPIR lead working with other PPIR leads from local NIHR-funded infrastructures. PPIE are described in detail in *Chapter 1*.

Tables 7, *8* and *28* summarise demographic data for screened and consented patients with respect to white and non-white ethnicity in the SPACE study.

Of the total population screened across the three centres, 60–67% of patients were female while 7–21% were of non-white ethnicity. While the latter data are broadly representative of the current UK population, in this study it was skewed by the limited recording of ethnicity at one of the centres. The haematology-oncology group had a relatively higher proportion of non-white ethnicity but otherwise, proportions screened in the 3 patient groups were similar in the proportions of females, non-white ethnicity and those 60 and over. In the group who underwent DPC, similar proportions were represented as in the overall population initially screened. Around half de-labelled were female, half were aged 60 and over and 10% were recorded as being of non-white ethnicity.

Recommendation for future research

Future research priorities

Although fewer patients underwent therapeutic de-labelling as compared with opportunistic de-labelling, the overall safety of this approach across both settings has been demonstrated in this study and previous systematic reviews.[9,34] There are a number of barriers and enablers to widespread roll-out of DPC in the different patient groups studies (acute medicine/ID, haematology and oncology patients and the perioperative population).

Based on these findings, we suggest that future research should focus on a multicentre randomised controlled trial with longitudinal follow-up to capture and quantify the impact on antibiotic use, primary care consultations, hospital admissions, hospital-acquired infections, perioperative anaphylaxis and mortality. Such a trial framework would enable the following additional questions to be answered:

- Are current recording systems employed in the NHS fit for purpose to accurately capturing adverse drug reactions including allergies?
- What are the most effective implementation strategies for the roll-out of DPC in a range of patient groups and clinical settings?
- The learning curve for carrying out risk stratification may vary depending on the background of triaging individuals. What training is required for different HCPs to become comfortable to be able to identify, risk stratify and de-label patients with a PAL in a range of secondary care patient groups?
- What are the key elements of an optimal risk-stratification pro-forma?
- What should effective staff training packages include?
- How can drug allergy education effectively be delivered for nurses, pharmacists, doctors, other HCPs during their training?

TABLE 28 Demographics of screened patients (ethnicity-wise)

	ALL			AMU/IDU			Presurgical			Haematology-oncology		
	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds	B'ham	Oxford	Leeds
N	796	472	990	182	229	489	362	208	422	251	35	79
Gender												
M (%)	262 (33)	189 (40)	383 (39)	58 (32)	99 (43)	167 (34)	107 (30)	74 (36)	185 (44)	97 (39)	189 (40)	31 (39)
F (%)	533 (67)	283 (60)	607 (61)	124 (68)	130 (57)	322 (66)	255 (71)	134 (64)	237 (56)	154 (61)	283 (60)	48 (61)
Ethnicity												
White (%)	517 (65)	375 (79)	819 (83)	122 (67)	197 (86)	399 (82)	240 (66)	156 (75)	355 (84)	155 (62)	22 (63)	65 (82)
Non-white (%)	100 (13)	97 (21)	64 (7)	22 (12)	32 (14)	31 (6)	50 (14)	52 (25)	28 (7)	28 (11)	13 (37)	5 (6)
Not recorded (%)	179 (23)	0 (0)	107 (11)	38 (21)	0 (0)	59 (12)	72 (20)	0 (0)	39 (9)	68 (27)	0 (0)	9 (11)

- What happens following the removal of the PAL? Do patients become 're-labelled' during subsequent interactions with health care either incorrectly or due 'true' allergic reaction/s? Are there staff training needs specifically associated with this aspect?
- What difference does de-labelling make in terms of longitudinal antibiotic use and hospital outcomes?
- Considering the 'hub and spoke' model, with a regional centre supporting smaller Trusts without an allergy specialist; what specifically is needed to address the safety of this approach alongside a fit for purpose governance framework and appropriate protocols.
- What are the long-term clinical outcomes and health economics surrounding penicillin allergy de-labelling to enable commissioners make informed decisions regarding long-term strategic planning?
- Is widespread roll-out of DPC cost-effective in all secondary care patient groups or are some clinical contexts better suited to this intervention?

Additional information

CRediT contribution statement

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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

Data are owned by the study sponsor (University Hospitals Birmingham NHS Foundation Trust) as per the collaborator agreement. All data requests should be submitted to the corresponding author (m.t.krishna@bham.ac.uk) for consideration and for sponsor approval. Access to anonymised data may be granted following a review of the request and will involve data sharing agreement with the requestor.

Ethics statement

This study was approved by The London Bridge Ethics Committee (REC Reference 21/PR/0814; IRAS project ID: 293544) on 23 July 2021.

Information governance statement

University Hospitals Birmingham NHS Foundation Trust, Oxford University Hospitals NHS Foundation Trust, Leeds Teaching Hospitals and University College London Hospitals NHS Foundation Trust are committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University Hospitals Birmingham NHS Foundation Trust is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (InformationGovernance@uhb.nhs.uk).

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/MTYW6557.

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Publications

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