FULL/LONG TITLE OF THE STUDY

A Multicentre Study to Investigate a Protocol-Driven Multidisciplinary Service Model to Tackle 'Spurious Penicillin Allergy' in Secondary Care (SPACE study)

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SHORT STUDY ACRONYM

SPACE Study

PROTOCOL VERSION NUMBER AND DATE

Version 14.0 09 Jun '22

RESEARCH REFERENCE NUMBERS

IRAS Number:	293544
SPONSORS Number:	RRK7186; EDGE ID 126756
FUNDERS Number:	NIHR129069

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1.0 SIGNATURE PAGE

I undersigned confirm that the following protocol has been agreed and accepted and the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's standard operating protocols, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
..../...../.....

Name (please print):

……

Position:
.....

Chief Investigator:

Signature: Date:
..../...../.....

Name: (please print):

Professor Mamidipudi Thirumala Krishna

2.0 KEY STUDY CONTACTS

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Committees	Study Steering Committee:

	1. Dr Guy Scadding, Consultant Allergist; The Royal Brompton Hospital, London; g.scadding@rbht.nhs.uk 2. Dr Linda Nel, Consultant Anaesthetist, Southampton University Hospitals NHS Trust; Linda.Nel@uhs.nhs.uk 3. Mr Alexander Thompson, Research Fellow in Health Economics, University of Manchester; alexander.thompson@manchester.ac.uk 4. Ms Kate Hopkinson, Senior Allergy & Immunology Nurse, Nottingham University Hospitals NHS Trust; kate.hopkinson@nuh.nhs.uk 5. Ian Clarke, PPIE member, Ianmaryclarke@sky.com Data Monitoring and Ethics Committee: 1. Dr Ravishankar Sargur; Consultant Immunologist; Sheffield Teaching Hospitals NHS Trust; Ravishankar.Sargur@nhs.net 2. Dr Iain McCullagh, Consultant Anaesthetist, Newcastle Hospitals NHS Foundation Trust; i.mccullagh@nhs.net 3. Dr Tim Planche, Consultant Microbiologist, St George's University Hospitals NHS Foundation Trust; tim.planche@nhs.net 4. Dr Jason Oke, Senior statistician, University of Oxford; jason.oke@phc.ox.ac.uk

3.0 STUDY SUMMARY

Study Title	A Multicentre Study to Investigate a Protocol-Driven Multidisciplinary Service Model to Tackle 'Spurious Penicillin Allergy' in Secondary Care (SPACE study)
Internal ref. no. (or short title)	SPACE Study
Study Design	A multi-centre pragmatic observational study employing combined qualitative and quantitative approaches
Study Participants	Total number of Direct Oral Penicillin Challenges (DPC) = 122 across the 3 centres in the following clinical settings 1. Acute Medical Unit and Infectious Diseases Unit 2. Haematology-Oncology Unit 3. Pre-surgical unit Clinical staff and stakeholders ~10 individuals at each site Study sites: 1. University Hospitals Birmingham NHS Foundation Trust 2. Oxford University Hospitals NHS Trust 3. Leeds Teaching Hospitals NHS Trust

Planned number of DPC(if applicable)	Total N=122
Follow up duration (if applicable)	5 days or a full clinical course as per clinical indication
Planned Study Period	24 months
Research Question/Aim(s)	Primary: ● To explore behaviour, attitudes and acceptability of patients, healthcare professionals and managers regarding use of DPC in 'low risk' patients ● To develop treatment pathways and a governance framework for this service model Secondary: ● To assess the proportion of 'low risk' patients with a PenA label 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 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

4.0 FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR (HS&DR funding stream)	£1,064,791.06 (research costs); £35,133.90 NHS support and treatment costs)

5.0 ROLE OF STUDY SPONSOR AND FUNDER

University Hospitals Birmingham NHS Foundation Trust is the sponsoring organisation and will formally delegate specific sponsoring roles to the Chief Investigator but remains legally responsible for the study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEE

Name	**Host organisation**	**Role**	**Email**
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Mrs Amena Warner	Allergy UK	PPI representative	amena@allergyuk.org
Dr Ron Daniels	CEO, The UK Sepsis Trust	Patient advocate	ron@sepsistrust.org

6.0 PROTOCOL CONTRIBUTORS

This protocol was developed by the investigators (see previous page, under study management group for details).

This project had input from Mrs Amena Warner (Allergy UK) and Dr Ron Daniels (CEO, The UK Sepsis Trust) in all aspects.

The investigators also consulted with patients (service users) for their views, perspectives and experiences with penicillin allergy labelling and de-labelling pathways.

This study is funded by HS&DR funding stream (NIHR) and underwent a rigorous process of external peer review.

The funder did not have (and will not have) any direct input into study design, conduct, data analysis, interpretation, manuscript writing and dissemination of results.

The funder does not control the final decision regarding any aspect of this study.

The investigators will keep the funder informed regarding the progress of the study and produce a final report upon completion.

7.0 KEY WORDS

penicillin, allergy, spurious,
anaphylaxis, antimicrobial stewardship,
antimicrobial resistance, de-labelling

8.0 ABBREVIATIONS

AMR: Antimicrobial resistance

AMU: Acute Medical Unit ; including patients admitted as an acute medical emergency on other wards within the hospital

ATC: Anatomical and Therapeutic Classification

CAPA: Corrective and Preventative Action Plan

CI: Chief Investigator

COPD: Chronic Obstructive Pulmonary Disease

COVID: Coronavirus Disease

CRN: Clinical research Network

DDD: Defined Daily Dose

DM(E)C: Data Monitoring (Ethics) Committee

DPC: Direct Oral Penicillin Challenge

DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

EP: Electronic prescribing

EVPI: Expected Value of Perfect Information

EVPPI: Expected Value of Perfect Parameter Information

GDPR: General Data Protection Regulation

GP: General Practitioner

HCP: Healthcare professional

HRA: Health Regulatory Authority

HSR: Hypersensitivity Reaction

ICER: Incremental Cost-Effectiveness Ratios

ICJME: International Council of Journal Medical Editors

ID: Infectious Disease

ISPOR: International Society for Pharmacoeconomics and Outcomes Research

NHS: National Health Service

NICE: National Institute for Care and Health Excellence

PenA: Penicillin allergy

PI: Principal Investigator

PPI: Patient and Public Involvement

R&D: Research and Development

REC: Research Ethics Committee

RN: Research Nurse

SD: Standard Deviation

SMC: Study Management Committee

SSC: Study Steering Committee

TENS: Toxic Epidermal Necrolysis

UCLH: University College London Hospitals

UHB: University Hospitals Birmingham

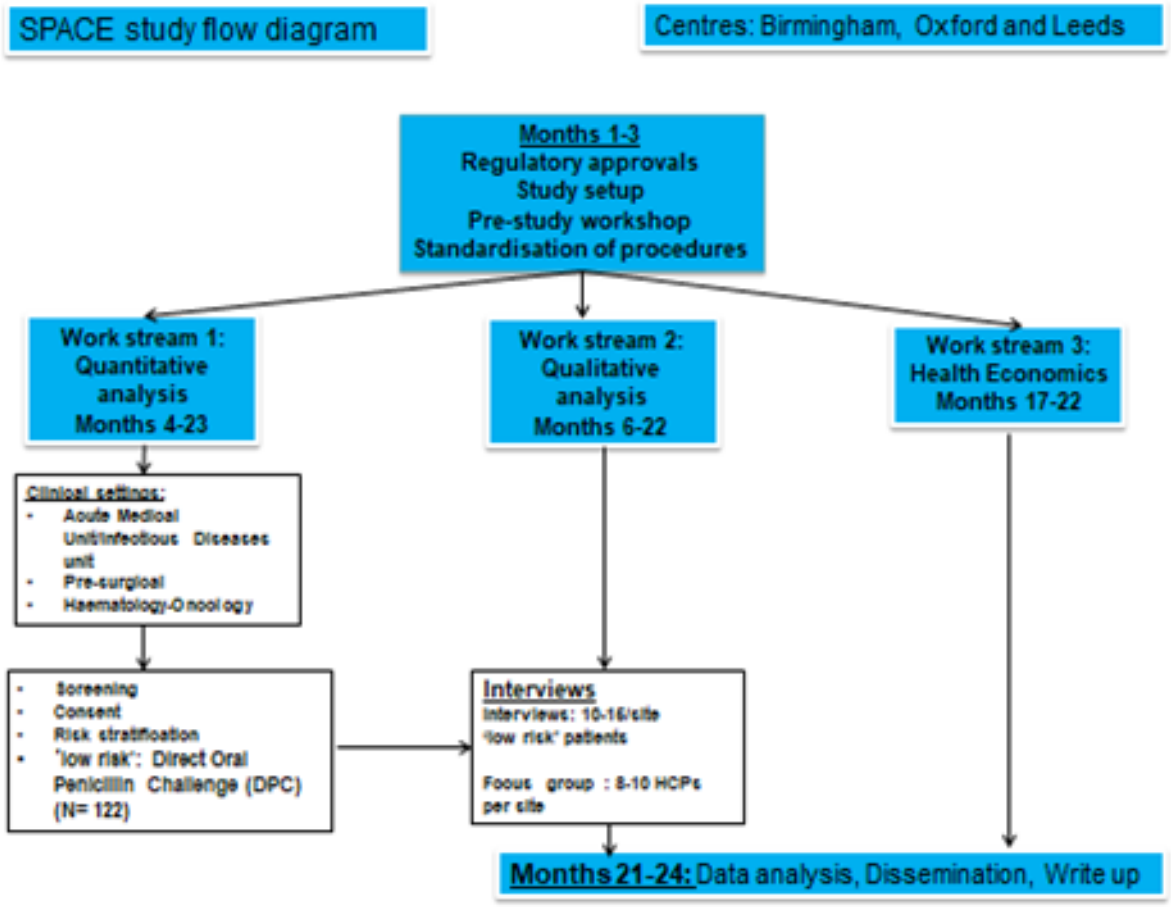
UK: United Kingdom

USA: United States of America

WHO: World Health Organisation

WS: Workstream

9.0 STUDY FLOW CHART



10.0 STUDY PROTOCOL

10.1 BACKGROUND

In preparation of this application, a literature search was performed to examine the existing evidence and current practices. The search was initially performed in June and September 2018 and repeated on 18 September 2019 using the following criteria: English language only; humans; last 10 years; PubMed search engine; MESH key words: penicillin allergy (yields 904 articles), AND testing, de-labelling, AND health costs, implications, health benefits, AND pre-operative patients, surgical patients, surgery, AND testing strategies. A 10year limit was set on the basis that much of the work informing these guidelines has arisen in this period of time. A total of 301 articles were selected; 93 were deemed relevant after a review. Additional articles were included on the basis of relevance, including some from more than 10 years ago where these were judged to be of seminal importance.

The investigators have published four narrative reviews[1-4] as well as qualitative and observational studies[5-11] directly relevant to this research proposal.

Problem: Six percent of the general population[8] in England and 15-20% of inpatients[12,13] carry a penicillin allergy (PenA) label. However, 90-95% of these labels are shown to be incorrect following comprehensive allergy testing[1,9,14-16]. Penicillins are the first-line antibiotic choice for many infections and are the most commonly prescribed antibiotics. PenA labels are a major barrier to antimicrobial stewardship. The applicants and others reported higher rates of antimicrobial resistance (AMR) and serious hospital infections in patients with documented 'PenA' in two UK population-based studies[8,17].

The assessment process for PenA currently involves a systematic clinical history, review of previous records, skin testing, and a supervised penicillin oral challenge [if skin testing is negative][18]. Oral penicillin challenge is the definitive method to exclude an allergy and confirm tolerance[18]. However, PenA testing is labour intensive, time-consuming, and requires a specialist in allergy. Given the burden of PenA and huge unmet demand for allergy services, PenA tests are not routinely available to inpatients[19-23]. Most hospitals in the National Health Service (NHS) do not have a specialist allergy service[21-23]. 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[18,24].

Current standard care therefore involves administration of second line broad spectrum antibiotics in PenA labelled patients. These are more expensive, lengthen hospital stay, increase readmission rates, and PenA labels have been associated with an enhance risk of AMR, surgical site infections, and other serious infections such as Methicillin Resistant *Staphylococcus aureus*, *Clostridioides difficile* and Vancomycin Resistant *Enterococcus*[10,17,25,26]. The lead applicant's team investigated the impact of

PenA labels on management of sepsis and performed a pharmacoeconomic analysis[27]. Data was systematically extracted from electronic medical records for adults admitted with sepsis in 3 acute care hospitals in Birmingham. One hundred sepsis episodes were analysed (n= 50 with PenA; n=50 non-PenA labels)[27]. **'**Sepsis 6 treatment' criteria were less frequently met in PenA group in comparison to non-PenA, specifically for the administration of first dose intravenous antibiotics within an hour after diagnosis[27]. Patients with a PenA label were more likely to receive carbapenems and 6-fluoroquinolones[27]. The antibiotic burden as assessed by the WHO/Anatomical Therapeutic Chemical (ATC) Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no/ddd/definition_and_general_considera/) standardised defined daily dosing (DDD) system was significantly greater in PenA group ($p<0.0001$)[27]. The cost of first dose and whole treatment course for antibiotics was 2.17 and 2.61fold greater respectively in the PenA group ($p<0.001$)[27].

Furthermore, the National Audit Project-6 conducted by The Royal College of Anaesthetists reported a higher relative risk of anaphylaxis to teicoplanin, an antibiotic given for surgical prophylaxis to patients with a PenA label[28]. Hence, 'spurious PenA' is now recognised as a major public health problem and there is an urgent need to put in place measures to mitigate its adverse impact.

This proposal brings together a group of experienced multidisciplinary clinical and academic experts, patients de-labelled in Birmingham and Leeds, and patient organisations with a wealth of experience in areas relevant to this project.

This research topic is of major strategic importance to all disciplines treating common and serious infections in hospitals and the study is likely to enhance the quality of antibiotic prescribing and quality of care, reduce rates of serious hospital-acquired infections and AMR, and reduce NHS costs in the order of several million pounds per year. AMR was put on the national risk register (www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-2) by the Chief Medical Officer in the UK and was declared as a high priority area by the United Nations in its 2016 resolution (www.gov.uk/government/news/uk-secures-historic-un-declaration-on-antimicrobial-resistance). This study is essential to explore the acceptability of patients, healthcare professionals (HCPs) and service managers regarding the proposed intervention and provide data to support adoption of PenA de-labelling across the NHS.

10.2 RATIONALE

10.2.1 Importance of this research

Given the burden of 'spurious PenA' and its adverse impact on health care, there is a clear need for safer and more cost-effective interventions to administer penicillins to those who are not allergic.

We and others have shown that PenA labels can be removed in a significant proportion of patients on the basis of clinical history and review of previous prescription records. We reported[9,10] that 40-60% of patients with a PenA label have a symptom pattern that is 'non-specific', i.e., not in keeping with a 'true' allergic reaction, and that 20% of patients with a PenA label had tolerated a penicillin since they were labelled but had not had their records amended[10]. Such patients are classified as 'low risk', and there is emerging evidence in favour of a 'direct' oral penicillin challenge (DPC) under medical supervision for this group, i.e., giving penicillin under supervision without performing PenA skin tests[2]. This approach was welcomed by the lead applicant's Trust senior management and a multidisciplinary audience comprising of physicians, nurses, pharmacists, microbiologists and managers. The lead and joint lead applicants have presented this topic locally (Trust Antimicrobial Committee, Trust Management, Grand Rounds), regionally (West Midlands Physician Association) and at national meetings (UK Drug Allergy Meeting and British Society for Allergy and Clinical Immunology) and sought critique and feedback that have helped shape this proposal. Awareness and challenges regarding the adverse impact of PenA labels on healthcare was evident amongst these audiences and there was a strong interest in the establishment of a PenA de-labelling service, including DPC to tackle 'spurious PenA'. However, the need for conducting this research was also acknowledged.

In a survey conducted by the applicants involving 193 staff (58% doctors, 31% nurses, and 11% pharmacists) in a busy district general hospital, 99% recognised 'spurious' PenA labels as a problem, and were willing to employ a validated tool to de-label patients, although there was also some anxiety expressed[11]. In a qualitative study conducted in primary care, the applicants found that general practitioners (GPs) were reluctant to amend patient records of PenA based on their clinical judgement and were uncertain regarding referral criteria for PenA testing[5]. This problem is compounded by sub-optimal and heterogenous allergy training in UK medical schools[29].

This research proposal investigates the role of a DPC in secondary care PenA de-labelling service. It is novel, distinct and complements the ongoing ALABAMA study (NIHR PGfAR) that focuses on benefits of proactive primary care referrals to allergy clinics for PenA de-labelling by a specialist.

10.2.2 Proposed model

The proposed service model for PenA de-labelling in secondary care is as follows:

Using information captured from a structured drug allergy history and review of previous prescription records (where available), patients will be stratified into 'low risk' and 'high risk[1,6,14]. The 'low risk' group will include those describing non-specific symptoms or a 'benign rash' that is not in keeping with an allergic reaction, or those with an 'indeterminate history' >10 years previously that is suggestive of a non-life threatening reaction. The 'high risk' group includes those with a history suggestive of an immediate allergic reaction or anaphylaxis (serious allergic reaction). Patients giving a history of serious immunological reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, Steven Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), erythema multiforme, etc., are excluded. Patients meeting criteria for 'low risk' will be offered a DPC. Those declining DPC and patients in the 'high risk' group will be referred to an allergy clinic as per current national guidelines[18,24]. The risk stratification process is performed by a senior research pharmacist (RP) or a senior research nurse (RN) who have undergone study-specific training and supervised by a consultant.

10.2.3 Review of evidence

This topic has been reviewed by the applicants[1-4] and others[14,16]. This multidisciplinary approach is underpinned by a relatively simple guideline-based risk stratification process[1,6,14]. Alongside, there is a need for a validated treatment pathway supported by an appropriate governance framework.

Our preliminary work and recent evidence from USA, Australia and New Zealand have shown that multidisciplinary PenA de-labelling pathways employing a risk stratification process including a DPC is a promising approach to improve antimicrobial stewardship and reduce healthcare costs[6,30-32]. However, there are some gaps in our understanding in some highly relevant areas relating to this model. Further insight is required into the following:

(a) behaviour/perceptions of patients/HCPs in secondary care regarding this approach
(b) time and resource required to support the process
(c) views of senior management in secondary care

This knowledge will be crucial in delineating treatment pathways and governance frameworks.

We reported a high negative predictive value (94%) for a risk stratification algorithm in accurately identifying 'low risk' patients with PenA[9]. We also safely de-labelled 54 patients in a pre-operative

surgical setting and received positive patient feedback regarding DPC[6]. The risk stratification process was carried out by trained staff nurses and overseen by an anaesthetist with expertise in PenA de-labelling. Another study from New Zealand reported safety of a similar approach in an inpatient setting with risk stratification performed by trained pharmacists[30]. Blumenthal et al. employed a similar model in Harvard group of hospitals on the medical wards and reported its safety and enhanced prescription rates for penicillins and other betalactam antibiotics by 7-fold[33]. The projected cost saving was $8.3-13.4m USD *per annum* in the Harvard group of hospitals[16]. Similarly, the lead applicant's group reported that their Trust incurred between £250-500k annually for alternative antibiotics in PenA labelled patients[10]. The applicants have published a narrative review[2] of recent studies[6,30,31,33-35] attesting to the safety of a DPC in 'low risk' patients.

In summary, there is strong evidence to support the use of a DPC in 'low risk' patients with PenA. However, understanding the views and perceptions of this intervention amongst patients, HCPs, and service management in different clinical settings within secondary care will be paramount to put in place appropriate patient pathways, protocols, resources and a clinical governance framework to enable widespread adoption of PenA de-labelling in the NHS. It is likely that this service model can be embedded into routine clinical care and will facilitate delivery of a superior antimicrobial stewardship and save costs for the NHS in the order of several million pounds annually.

10.3.0 Objectives

10.3.1 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.

10.3.2 Secondary

- To assess the proportion of 'low risk' patients with a PenA label 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 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.

10.3.3 Outcome

Primary:

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

Secondary:

a. % of patients stratified as 'low risk' and 'high risk'.
b. % of 'low risk' patients willing to undergo DPC.
c. % of 'low risk' patients safely negotiating DPC.
d. Description of adverse events if any.
e. Development of 'fit for purpose' IT systems and cascading allergy status to primary care.
f. Clinical governance framework including leadership and defining roles for membership of multidisciplinary team.
g. Audit tools.
h. Health economic modelling to explore cost-effectiveness and help in strategic planning for hospital managers.

10.4.0 STUDY DESIGN, METHODS OF DATA COLLECTION AND DATA ANALYIS

10.4.1 Study Design

This is a multi-centre study employing a combined qualitative and quantitative approach and involves three workstreams (WS).

10.4.2 Setting

This study will be conducted at the following sites over 24 months. Recruitment will take place 8am – 5pm, Monday – Friday, excluding bank holidays.

Site	**Principal Investigator**
University Hospitals Birmingham NHS Foundation Trust	Professor M Thirumala Krishna
Oxford University Hospitals NHS Trust	Dr Siraj Misbah
Leeds Teaching Hospitals NHS Trust	Dr Louise Savic

The intervention will be investigated in three clinical settings at each site including:

1. Acute medical unit (AMU; including patients admitted as an acute medical emergency on other wards within the hospital)/infectious diseases (ID) units.
2. Haematology-Oncology unit.
3. Pre-surgical assessment unit.

10.4.3 WS1

10.4.3.1 WS-1 objective:

1. To provide a demographic description of PenA labels in AMU/ID units, Haematology-Oncology units and pre-surgical units.
2. To provide reasons for failure to progress from triage to DPC.
3. To determine the mean time taken to complete screening log and risk stratification proforma.
4. To determine the proportion of study eligible patients stratified as 'low risk' and 'high risk'.
5. To provide a descriptive analysis of DPC uptake and outcomes.
6. To determine the proportion of patients meeting national criteria for referral to an allergy specialist for PenA skin tests.

10.4.3.2 Inclusion and exclusion criteria for initial triage process:

Inclusion criteria:

Patients with a current PenA label, ≥18 years, willing and able to give informed consent

Exclusion criteria:

- Clinically unstable patients, i.e., unstable cardio-respiratory status (eg: respiratory failure, cardiac failure, pre-hepatic encephalopathy etc.)
- History of serious non-immediate systemic hypersensitivity reactions (HSRs) to penicillin
    - *Documented Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TENS), acute exanthematous generalised pustulosis (AEGS), erythema multiforme, haemolytic anaemia, vasculitis, acute interstitial nephritis*
- Those deemed unsuitable for medical reasons (unlikely to comply with study protocol)
- Pregnant
- Breast feeding
- Concomitant COVID-19 infection (patients from pre-surgical units and Haematology-Oncology units may be considered following recovery from COVID-19)

- Those participating in any other research currently or those who have participated in research involving medicinal product, medical devices and/or other intervention in preceding 6weeks.
- Patients currently receiving Omalizumab or those who have received Omalizumab within 6 months prior to proposed DPC
- Patients currently taking antihistamine and are unable to temporarily withdraw this medication for the proposed DPC

10.4.3.3 Patient identification & recruitment, risk stratification, DPC and data analysis

AMU ; including patients admitted as an acute medical emergency on other wards within the hospital */ID units:*

Patient Identification for participation: A list of inpatients with PenA labels will be generated from the Trust electronic prescribing (EP) system (or other information systems available at study sites) on a daily basis and patients will be triaged (see Appendix-11.01 for proforma) to determine eligibility for inclusion for risk stratification. This process will be conducted by the research nurse (RN)/research pharmacist (RP) (deemed part of direct clinical care team by respective participating Trusts) in liaison with respective clinical teams. The triage list will subsequently be pseudo-anonymised and stored as an electronic document within the Trust, in a site file accessible only by the study team. Triaging will be carried out Monday-Friday (excluding bank holidays) during working hours (8am-5pm).

Informed consent and Risk stratification:

A list of patients meeting initial triage criteria will then be forwarded by the RN/RP performing the initial eligibility screening to the RN or RP conducting the risk stratification process for a DPC. Having sought permission from the clinical care team, the RN/RP will approach patients and give them a patient information sheet (Appendix 11.02). A minimum period of 4-6 hrs will be given for them to consider participation and prior to informed consent. Patients will also be given an option to take additional time for consideration to participate. In those patients where the clinical care team identify a need of urgency for the administration of a penicillin antibiotic and/or in those who are keen and have understood the information provided regarding this research study, informed consent will be sought within an hour after the patient information sheet is issued. This will align well with the rapid turnaround times within acute medical unit and offer opportunities for opportunistic and therapeutic delabelling. The RN/RP will then return to the wards and ask the patient if they wish to participate in the study. An informed consent (Appendix-11.02) will be obtained by RN/RP at this stage prior to systematic stratification as 'low risk' and 'high risk' (described in later section). This will be conducted by RPs who have undergone study-specific training in Oxford and Birmingham sites and RNs who have undergone study-specific training in Leeds. Evidence of training will be documented in the respective site files. A nominated Consultant Physician will provide clinical support to the RP/RN. The risk stratification process will be standardised on a proforma (Appendix-11.03) across all sites and appropriate training delivered to the study team at a pre-study workshop. A paper copy or an electronic copy of the duly signed consent form will be

forwarded by the research team to patient's general practitioner by post or electronically respectively and the patient will be made aware of this prior. A copy of the consent form will be filed in patient's hospital notes or electronic records at respective site files. Consent will also be documented in hospital notes.

We will display posters (Appendix – 11.04) in these units to advertise the study.

Pre-surgical and Haematology Oncology units: A list of patients with PenA labels will be generated from the Trust electronic prescribing (EP) system (or other information systems available at study sites) by the RN/RP (deemed part of direct clinical care team by respective participating Trusts) and patients will be triaged (see Appendix-11.01 for proforma) to determine eligibility for inclusion for risk stratification. Initial triage process will be conducted by the RN/RP (deemed part of direct clinical care team by respective participating Trusts) in liaison with respective clinical teams. We will display posters (Appendix – 11.04) in these units to advertise the study. For patients who are attending face-to-face consultations, permission will be sought from respective clinical care team before the research team approaches the patient. A patient information sheet will be issued to the patient (Appendix 11.02).

For those patients who are not attending face-to-face consultations, the RN/RP will contact the patient directly by telephone to introduce the study and seek permission to forward the patient information sheet by post and/or email.

The patient will be advised to contact the research team directly or inform their clinical care team to express interest in participation or alternatively permission will be sought from the patient for the research team to contact them *via* telephone after 48 hours to ask if they wish to participate. If agreeable to the patient, the research team will take an opportunity to discuss the study with the patient. Depending on circumstances and patient preference, this may be done either on the same day or at a mutually convenient appointment, either face-to-face or remotely (virtual or *via* telephone). If the patient confirms interest in participation, their details will be forwarded to RN or RP organising/conducting risk stratification and DPC, so this process could be facilitated.

The study RN or RP will obtain an informed consent (this may be a verbal consent at this stage but will be recorded in the study documentation) prior to risk stratification. This will be conducted either in an interview face-to-face or on a virtual platform or *via* telephone. Those consenting over telephone or virtually will be advised to email or post the signed consent form to the study team in a prepaid self-addressed envelope or bring it with them to the DPC appointment. A paper copy or an electronic copy of the duly signed consent form will be forwarded by the research team to patient's general practitioner by post or electronically respectively and the patient will be made aware of this prior. A copy of the consent form will be filed in patient's hospital notes or electronic records and at respective site files. Consent will also be documented in hospital notes.

Patients will be risk stratified by RN or RP as described in previous section, and those deemed 'low risk' will be invited for a DPC on an elective basis. There will be a nominated Consultant Physician and Consultant Anaesthetist providing clinical support and clinical cover to RN/RP for Haematology Oncology units and pre-surgical units respectively.

Inclusion and Exclusion Criteria for DPC:

Risk stratification process: This will be conducted using a standardised proforma and criteria (summarised in the next section; Appendix 11.03). This will also involve review of previous prescription and health records or/and a phone call to patient general practice (GP) surgery for additional clarification as deemed necessary. Patients will be stratified as 'low risk' and 'high risk'. The risk stratification criteria are adapted from a system described by us and others previously[1,6,14]. This is as follows:

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

- history of nonspecific symptoms *only* (eg: headache, isolated dizziness, gastrointestinal symptoms).
- Thrush *only*, no other symptoms.
- mild 'benign#' rash.
- History of 'childhood rash – no further details available'
- Pruritus without rash.
- those with gaps in clinical history, but history is 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 PenA label.
- No history of an 'index episode' but has been advised to avoid penicillins due to family history.

#benign rash: Check list for a 'benign' rash - should satisfy all of the following:

- ✔ *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 are not satisfied or relevant information is not available, patient will be stratified as 'high risk' (see below).

High Risk (not for DPC): Those with any one or more of the following:

- severe, uncontrolled or brittle asthma.
- severe 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 or treatment.
- history of angioedema as a part of index reaction.

Those classified as 'low risk' and deemed suitable as per study criteria will be invited to participate in a DPC. A DPC will be conducted following approval of the nominated consultant as described above. In patients stratified as potentially 'low risk', but where a DPC cannot be conducted during their inpatient stay whether for clinical or logistical reasons, or due to patient preference, an appointment will be arranged for the DPC to be conducted electively as an outpatient procedure. The risk stratification status will be reconfirmed prior to DPC in these patients.

All patients, including those who do not agree to undergo DPC will be invited to participate in the interview study (see section 4.4, work stream 2) at this stage.

The RN or RP will contact the pre-surgical patients and Haematology-Oncology patients either via virtual platform or telephone or visit them on the wards, outpatients or day units (this depends on the patient's clinical situation) for risk stratification process and informed consent. Those contacted by telephone or *via* virtual platform will be advised to bring the signed informed consent to their appointment for DPC or send it by email or post in a prepaid stamped self-addressed envelope. DPC will be conducted electively and the patient will be given adequate notice regarding the appointment. Details of patients wishing to participate in WS 2 for 1-1 interviews will be forwarded to relevant research personnel.

Furthermore, the RN and RP will also seek permission from the respective consultant in-charge of patient's care prior to enrolling the patient into this research.

The following generic data will be captured regarding the following at each study site:

- *Number of patients triaged or screened.*
- *Number of patients stratified as 'low risk' and 'high risk'.*
- *Proportion of 'low risk' patients that agreed to undergo DPC and/or interview study.*
- *Time taken for informed consent process.*
- *Time taken to conduct DPC including completion of study documentation and follow up.*
- *Proportion of DPC tested patients deemed test negative.*
- *Proportion test negative patients whose hospital electronic health record is updated.*

DPC procedure: This procedure will be carried out in a safe clinical environment under clinical supervision with immediate access to cardiopulmonary resuscitation and access to a critical care team. A standardised proforma will be used to capture data (Appendix – 11.05).

Steps for DPC are listed as follows:

1. The research team will confirm that antihistamines have not been taken during the 3 days prior to the DPC
2. A urine pregnancy test should be performed for female participants of child bearing potential prior to commencing the DPC. If the test is positive, the participant will be excluded from the study.
3. Check baseline vital parameters (heart rate, blood pressure, SPO_2).
4. .After confirming patient suitability with study consultant, administer oral amoxicillin (single dose 500mg).
5. Monitor patient signs and symptoms of allergy for 60 minutes following DPC.
6. Repeat vital parameters.
7. Complete study proforma.

Patients will receive 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-1 HSR. This will involve discussion between research team and respective clinical team.

Alternatively, in those who do not require penicillin (opportunistic de-labelling) during current admission, a modest dose of 250mg twice daily for 3 days will be given. This is usually conducted for the following clinical scenarios:

1. temporal association is unclear from clinical history with respect to index reaction/s.
2. index reaction/s – delayed in onset, i.e., not after the first dose but occurs during a course of treatment (eg: day 2 or day 4 of treatment).

Patients who commence opportunistic de-labelling and then develop an intercurrent infection that requires a full therapeutic course of amoxicillin or an alternative penicillin antibiotic, could be switched to the appropriate treatment regimen following discussion between research team and respective clinical teams. The modest dose (250mg) of amoxicillin used for opportunistic de-labelling must be withdrawn/amended at this stage. This must be clearly recorded in the patient notes and in relevant study documentation

Follow up and advice (all patients):

- Patients will be provided with a 'participant note' (Appendix – 11.06) and counselled prior to discharge and provided with written guidance regarding seeking urgent medical attention (call 999) or calling their GP if needed. In those who have temporarily withdrawn antihistamine for the DPC, specific advice will be given by the research team regarding recommencement of antihistamine following completion of DPC.

- All patients will be either reviewed (if they are still an inpatient) or contacted *via* telephone or virtual platform (if discharged) on day 5 to establish clinical tolerance and exclude a delayed reaction. Patients will be contacted by the research team on the next working day, if day 5 follow up call falls on a weekend or a national bank holiday and this will be recorded in study documentation retrospectively. Patients will be advised to contact the research team in case they develop a delayed-onset symptoms either before or after day 5.

De-labelling and communication to patient and GP:

1. The outcome of the DPC will be discussed with the patient, communicated in writing via post or electronically to their GP (Appendix – 11.07) and hospital records updated accordingly. A 'wallet card' stating DPC outcome will be provided for patients.
2. For the 'high risk' group and those declining DPC, the outcome of risk stratification will be communicated in writing or electronically to their GP (Appendix – 11.07), to enable appropriate follow up in accordance with national guidelines[18,24].

WS-1 Output and data analysis:* Pseudo anonymised data will be entered at each study site on a standardised spreadsheet or other software programmes and the following descriptive statistics will be generated:

1. Demographics analysis including age, gender and ethnicity.
2. Total number triaged.
3. Analysis of reasons for failed progression from triage to DPC.
4. Time taken to complete screening log and risk stratification proforma.
5. Overall proportion stratified as 'low risk' and high risk'.
6. Overall proportion of 'low risk' that agreed to undergo DPC.
7. Overall proportion of patients declining to undergo DPC.
8. Proportion of those stratified as 'high risk' and 'low risk' (those declining DPC) meeting national criteria[18] for referral to an allergy specialist for PenA skin tests.
9. Outcome of DPCs:
    a. *Proportion successfully de-labelled.*
    b. *Description of adverse reactions (immunological or nonimmunological).*
    c. *Proportion of patients that did not complete DPC with description (eg: those that undergo first dose of DPC and then opt out of the study).*
    d. *Proportion of 'dropouts' with description (eg: those that express interest and default appointment at DPC).*
    e. *Proportion of immediate (including severity as per international grading system[37,38]) and nonimmediate HSRs (descriptive analysis) and other adverse reactions and treatment received.*

**Descriptive data regarding inter-site and inter-clinical setting will be summarised as N=(%)*

Patient pathways for WS1 are summarised in Appendices 11.08 and 11.09.

A total number of 122 DPCs will be conducted across the 3 participating centres in the above clinical settings. In the event that the recruitment targets are not met at an individual centre, other centres will aim to compensate with additional participants to achieve the proposed number of DPCs.

10.4.4 WS2: Qualitative work

Drs Jani and Williams will lead this WS and oversee a research assistant who will conduct the data collection and analysis.

10.4.4.1 Rationale

This WS complements the other WSs to investigate and understand the practicalities of implementing the PenA de-labelling intervention. As stated previously, the evidence base is under-developed in this area and our approach draws on qualitative research methods including semi-structured interviews and focus groups[39,40] to explore the diverse perspectives that may influence the development and implementation of the intervention and associated pathway.

10.4.4.2 Aim

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

10.4.4.3 Objectives

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

10.4.4.4 Methods

Semi-structured interviews and focus groups will be used to collect data on the behavioural insights and changes that may be required for the de-labelling intervention to be fully implemented.

Participants and sampling strategy:

Our target population is key stakeholders including patients, HCPs, operational managers, and commissioners who may influence individual or organisational factors implicated in the changes required for adoption of the new pathway. Inclusion criteria for participants will incorporate diversity in terms of gender, age and other characteristics. Patient interviews will begin at week 8 after WS1 to allow a period of set up and familiarisation and will be conducted at regular intervals as the intervention is introduced and embedded within the sites. Focus groups will be conducted midway through WS1 to allow a period of embedding.

a) Patients

Patients will be invited to participate in this WS at the time of recruitment for WS1 through WS1 co-research staff at each site and followed up by WS2 research staff to confirm participation and consent. Details including patients study identification number, email id and telephone number will be securely transmitted by WS1 research staff to WS2 research staff. The WS2 staff will delete email id and telephone numbers from their records after the interview has been completed (and email the patient to confirm accordingly).

An equal number of 'low risk' patients who have completed a DPC and those who declined the DPC will be invited for interview. Interviews will be conducted either face-to-face, or *via* virtual platforms or telephone. One-to-one semi-structured interviews will be conducted with patients using an interview schedule designed according to the aims and objectives stated above (Appendix-11.10). Interviews will explore individuals' understanding, willingness and experience regarding DPC. The interview questions will be informed by risk perception theories[41] and developed from relevant literature and the experience of the research team. The interview schedule will mainly comprise open questions to allow patients to provide their own perspectives, be iterated in consultation with our patient and public partners and piloted before use to ensure face validity.

We anticipate a total of 10-15 interviews at each site, although this will be subject to saturation checking[44]. Through targeted patient recruitment we will ensure, as far as possible, that the interview sample reflects diversity with respect to gender, age, ethnicity and any other characteristics identified as important during the data collection period.

b) Other stakeholders

We will convene focus groups (in person or online) with other stakeholders to gather collectively refined accounts of the wider behaviours and contexts affected by the proposed intervention[42]. We will purposively sample prescribers, pharmacists, nurses, microbiologists, allergy specialists, operational

and business managers, clinical leaders and commissioners for inclusion within each site. The relevant personnel will be invited to participate *via* internal emails from local PI as well as posters advertising the study in relevant clinical and non-clinical areas. A list of those interested in participating from different professional groups will be drawn up by the local PI and shared with the WS2 team in a secure fashion. Drs Jani and Williams will lead on selecting a sample of healthcare workers which best represents the widest range of views. Participants will sign an informed consent prior and this process will be coordinated by WS1 coordinator at respective sites. As data collection proceeds and we become aware of gaps in our knowledge, we may request that some participants snowball invitations to relevant colleagues. This process will be managed by the research team to ensure that we achieve our objectives.

Two members of the research team will facilitate the discussions using a topic guide and stimulus material relating to de-labelling will be used to prompt discussion. The focus group topic guide (Appendix-11.11 for topic guide, Appendix-11.12 for participant information sheet, Appendix-11.13 for Focus Group Consent Form) informed by relevant domains of the Theoretical Domains Framework[43], will enable discussion of participant views and perceptions regarding implementation of PenA de-labelling in routine clinical care.

As contextual factors may play a role at each site, we anticipate conducting at least one focus group per site, each comprising 8-10 participants (up to a total of 3 focus groups).

We will observe good research ethics conduct at each stage of recruitment and data collection.

10.4.4.5 Data collection and processing

Interviews will be arranged and conducted either whilst the patient is still in hospital or soon after discharge. Interviews will be conducted face-to-face (with appropriate COVID-19 precautions) or *via* telephone or virtual platform depending on patient preference. With the consent of the patient, interviews will be audio recorded, anonymised by the researcher and then transcribed verbatim by a professional transcribing service as soon as possible after conducting the interviews.

Focus groups will be held on each site to maximise participation, and we anticipate that they will last between 90 and 120 minutes. Focus group participants will be asked to fill in a short questionnaire on socio-demographic data and sign a consent form (Appendix –11.13) before the start of the focus groups. Focus groups will also be audio recorded and transcribed verbatim by a professional transcribing service.

All qualitative data will be entered into NVivo software (QSR International (UK) Limited, Southport, UK), a data management and analysis programme to enable the application of qualitative analytical procedures which employ a system of coding and memoing developed by Lofland and Lofland (1995).

10.4.4.6 Analysis

A full descriptive analysis will be conducted to meet study objectives. Interviews and focus group transcripts will be analysed using thematic coding mapped to the theoretical domains framework to understand the cognitive, affective, social, environmental, organisational and professional influences on behaviours relating to PenA status de-labelling. The WS2 researcher will code emerging themes drawing on the theoretical frameworks that underpin the interview schedule and topic guide. An iterative approach using constant comparison will be employed in the development of coding frames and coding of data. A second WS2 researcher will read all the transcripts and code a sample to ensure reliability. Emerging themes will be discussed at team meetings and shared with our patient representatives to confirm that interpretations made by researchers stay close to the direct experience of patients.

Data handling: We will preserve participant confidentiality in accordance with the Data Protection Act 2018 and the General Data Protection Regulations 2018. Patients and stakeholders participating in WS2 will be assigned a unique identifier and all data will be anonymised and stored securely on University College London Hospitals (UCLH) NHS Foundation Trust premises using a secure drive to which immediate members of the project team will have access. Interviews and focus groups will be recorded using encrypted recording devices, with audio files securely stored on UCLH NHS Foundation Trust network servers. Transcription will be conducted by an institution-approved company, subject to a confidentiality agreement. Transcripts will be password-protected and stored on UCLH NHS Foundation Trust network servers. Consent forms will be stored in locked cabinets in a secure office within UCLH NHS Foundation Trust. In accordance with UCLH NHS Foundation Trust regulations, we will retain the anonymised research data for ten years in secure archives on UCLH NHS Foundation Trust premises, with Dr Jani as data custodian. At the end of the study, with participants' consent, data in the form of anonymised transcribed interviews will be stored in the [sponsor site – University Hospitals Birmingham NHS Foundation Trust] data repository and will be made available to bona fide researchers on request.

Outputs: This WS will generate insights into factors relating to organisational context, treatment pathway, protocol implementation, time taken and resources and contribute to understanding of the influences on patient and HCP behaviours, and perspectives of managerial and operational stakeholders in organisations. The findings will contribute to our 'stop/go' criteria (see 4.6).

10.4.5 WS3: Health Economic Modelling

Dr Ruben Mujica-Mota will lead this workstream and will be supported by a research fellow undertaking data collection and analysis.

Care pathway mapping: A care pathway mapping exercise (month 1), including the academic study team and clinical representatives from the three study sites will be conducted to fully map the respective clinical pathways for the proposed PenA de-labelling programme and current practice. Anticipated decision points where patient management will change and potentially impact on patient health will be identified, in addition to expected resource use required to deliver each aspect of the pathways. Differences in local management will be identified and consensus will be met on the pathway that will form the base case analysis and any regional differences that should be explored in scenario analyses.

Development of model structure and identification of model parameters: The comparative pathways mapped will inform the structure of the decision-analytic model and facilitate identification of the data required to parameterise the model (months 1-3). This information will be fed back to the wider study team to ensure that the necessary data are collected from study participants and local project managers.

Construction of decision-analytic model: A study team meeting (month 18) will be convened to re-present the decision-analytic model structure and explore whether the results from WS 1 and 2 have led to any changes to the proposed PenA de-labelling programme or highlighted any additional scenarios that we need to explore in the economic modelling. The model will then be constructed (months 18-24) in line with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) good practice recommendations[45]. The model will compare the cost-effectiveness of the proposed PenA de-labelling programme with current practice. The model will conceptualise patients passing through the pathway and allow estimation of the potential impact of introducing the PenA de-labelling programme on patient health and costs. Data from the study will be used to inform model parameters, including but not limited to patient characteristics, proportion stratified into 'low risk' and 'high risk' groups and DPC outcomes. A NHS and personal and social services perspective will be adopted, in line with NICE recommendations. Key model outcomes will include incremental cost-effectiveness ratios (ICERs) and net health benefit. Probabilistic analysis will be used to account for and describe uncertainty in model parameter estimates. Scenario analyses will be conducted to help understand the impact of any assumptions made or regional differences in patient management previously identified.

Value of information analysis: Based on our decision-analytic model, we will use value of information analysis[46] to estimate the expected value of perfect information (EVPI) which can be used to guide whether it is of value to collect further data to reduce the probability of making the 'wrong' decision. We will also calculate the expected value of perfect parameter information (EVPPI) which estimates the value of removing uncertainty in specific model parameters. These analyses will be used to help determine whether further research is needed and also guide future study designs.

Engagement with service managers: The results of the economic modelling will be presented to service managers at each of the 3 study sites to explore their perspective on the economic viability of the proposed PenA de-labelling programme and to ascertain what, if any, further evidence they would require to adopt the programme at their hospital.

10.4.6 'Stop/Go' criteria

A traffic light system will be followed to determine *a staged roll out of the intervention in the NHS* as per following metrics:

(Red – 'stop', Amber – 'review protocol by study steering group' and Green – 'Go').

1. Complete study documentation: >80% Green; ≥70-80% Amber; <70% Red.
2. Completed DPCs amongst recruited participants: >65% Green; 50-65% Amber; <50% Red.
3. 0% DPCs cause serious reactions – Green.
4. Conclusions from qualitative research are in support of this approach – Green.
5. *Other scenarios – 'Amber':*
    a. *DPCs cause serious reactions (i.e., serious cardio-respiratory compromise necessitating admission in intensive care unit, SJS, TEN, DRESS) – each adverse clinical outcome will be carefully reviewed and interpreted with respect to its timing, clinical context, severity, nature of index episode and patient feedback/perception. Based on our findings, inclusion and exclusion criteria and protocol for DPC will be amended by the investigators as deemed necessary either during the study or following its completion. Further external input from international experts or those from British Society for Allergy and Clinical Immunology (BSACI) will be sought if needed.*
    b. *Any concerns emerging from patients, HCPs and managers will be carefully considered and treatment pathways and governance framework ratified by the study steering group.*

10.4.7 Sample size calculation

Sample size calculation for DPCs: A recent systematic review (OP-JACR200125 1..10 (nih.gov) involving 1202 patients in 13 studies (inpatient and outpatient 'low risk' PenA cohorts) 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 are required across the 3 participating sites.

10.5 ETHICAL AND REGULATORY CONSIDERATIONS

10.5.1 Approvals

This study will commence after a favourable ethical opinion has been obtained from REC and global governance approval from the HRA. Prior to opening each centre to recruitment, the Chief Investigator will ensure that "Capacity and Capability" has been confirmed at each recruiting site.

10.5.2 Compliance

The study will be monitored and/or audited by University Hospitals Birmingham NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the UK Health Policy Framework for Health and Social Care.

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The study coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an on-going activity.

Once the quality assurance team have been informed of the first study participant being enrolled into the study and their first visit completed, the data and adherence to protocol will be monitored by the Sponsor's quality assurance Team. Monitoring of study participants by the Sponsors quality assurance team will then occur at random intervals throughout the study, this may be in the form of self-monitoring tools being supplied.

Study conduct will be subject to systems audit of the study record for inclusion of essential documents; permissions to conduct the study; study delegation log; curriculum vitae of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (eg: inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs. This will be led by the study co-ordinator and reported back to the Sponsor.

Entries on case record forms will be verified by inspection against the source data. A sample of case record forms (approximately 10%) will be checked on a regular basis for verification of all entries made. In addition, the subsequent capture of the data on the study database will be checked. Where corrections are required, these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority where applicable as required.

Non-compliances may be captured from a variety of different sources including monitoring visits, case record forms, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which will be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the R&D Office will agree an appropriate action by implementation of a Corrective and Preventative Action Plan (CAPA), including an on-site audit.

10.5.3 Amendments

All substantial and non-substantial amendments will be approved by Study Management Committee (SMC), Study Steering Committee (SSC) and Data Monitoring and Ethics Committee DM(E)C and following formal approval by study sponsor and REC. Appropriate documentation will be maintained with relevant version number of study documents and shared with all investigators.

10.5.4 Protocol deviations

All deviations will be immediately brought into attention of local PIs. Any significant deviations will be brought to the attention of CI and discussed with SMC, SSC, DM(E)C, study sponsor, and IRAS/REC formally communicated. Significant deviations will be investigated immediately and its potential impact on patient safety and data quality will be addressed. An audit trail of all relevant documentation will be maintained.

10.5.5 Adverse events

All adverse events will be captured and addressed by study investigators and local PIs. All serious adverse events (SAEs) will be addressed immediately giving patient safety 'high priority'. These will be immediately mapped with pre-determined 'stop-go' criteria. The study sponsor will be informed (usually within 24 hours) as soon as possible after patient safety has been addressed. All SAEs will

be discussed at the earliest opportunity with CI/co-CI and SMC, SSC and DMEC. All SAEs will be reported according to regulatory guidelines.

10.5.4 Peer review

This study has been subjected to rigorous peer review process under the HS&DR funding stream of NIHR. This involved review by multiple experts with a diverse professional background including those who hold expertise in specialist areas of this research.

10.5.5 Patient & Public Involvement & Engagement (PPIE)

The Clinical Lead (Mrs A Warner) of Allergy UK and Chief Executive Officer (Dr Ron Daniels) of The Sepsis UK Trust were involved in the development of the study design and protocol and are co-applicants of the NIHR grant funding this project. Furthermore, the investigators sought opinion of patients attending their clinic for PenA de-labelling and those who participated in a previous PenA de-labelling study. There will be continued PPIE in this study *via* local investigator meetings involving patient representatives and project meetings involving investigators between different participating sites.

10.5.6 Data protection and patient confidentiality

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act 2018, the General Data Protection Regulation (GDPR), NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care (2018), Research Ethics Committee (REC) approval and Health Research Authority (HRA) approval.

Patient identifiers including name, age and PID will be entered on study proforma which will be accessible only to research team at respective study sites and no external parties. The CI is the 'Custodian' of the data. The patients will be anonymized with regards to final data analysis and any future publications relating to this study. Enrolled participants will be allocated a unique study code number. This will be used for reference on research documentation transmitted outside respective study sites for data analysis by the research team based externally to ensure confidentiality. Only authorised members of the research team will have access to this research data. All research data will

be stored securely in adherence with the Data Protection Act (2018), the General Data Protection Regulation (GDPR) and Trust Confidentiality Policy.

Consent will be obtained to allow authorised staff employed by the sponsor to review identifiable data to ensure the study is monitored / audited to assess compliance with the protocol.

10.5.7 Data storage

All study-related documents will be securely stored in a locked cabinet in the respective participating study sites with access to authorised research personnel only. Relevant data will also be stored electronically in the respective Trust server and will be password protected and accessible to authorised personnel only. Study data will be encrypted and transmitted securely in anonymised fashion for data analysis to research team based externally. The study will be archived in line with the University Hospitals Birmingham NHS Foundation Trust's archiving policy. See section 4.4.4. for WS2 data storage.

10.5.8 Indemnity

University Hospitals Birmingham NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the CI and the NHS Trust taking part in this study. The non-commercial model clinical trials agreement will be used with all participating sites detailing their local responsibilities.

University Hospitals Birmingham NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

10.5.9 Access to the final study dataset

A master e-copy of final dataset will be stored securely in an encrypted format in R&D Department at University Hospitals Birmingham NHS Foundation Trust. Data will be transmitted in an anonymised encrypted format to statistician at the end of the study. Data collated from respective centres will be stored securely in an encrypted format in Trust server by respective R&D departments and paper copies of study will be stored in a locked fireproof cabinet and will be accessible to the respective study teams in their Trust.

10.6 Dissemination

The research team will endeavour to disseminate the results of this study *via* local, national and international scientific/clinical meetings and conferences and publish in peer review journals. No patient identifiable material will be published.

10.7 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be based on International Council of Medical Journal Editors (ICMJE). External agencies, i.e., outside the research team will not be involved in data analysis and write up.

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10.9 APPENDICES

1. Appendix-11.01: Initial triage (screening) proforma, i.e., patient identification for participation.
2. Appendix-11.02: Patient Information Sheet (PIS).
3. Appendix-11.03: Risk stratification proforma.
4. Appendix-11.04: Study poster.
5. Appendix-11.05: DPC proforma.
6. Appendix-11.06: Participant note.
7. Appendix-11.07: Model letters to communicate to general practitioner.
8. Appendix-11.08: Patient pathway for WS1 (AMU ; including patients admitted as an acute medical emergency on other wards within the hospital /ID units).
9. Appendix-11.09: Patient pathway for WS1 (Haematology-Oncology and Pre-surgical units).
10. Appendix- 11.10: WS2 patient interview schedule.
11. Appendix- 11.11: WS2 professional/stakeholder focus group topic guide.
12. Appendix- 11.12: WS2 invitation and participant information sheet for professionals/stakeholders participating in focus groups.
13. Appendix- 11.13: Consent form focus groups (WS2).

10.10 Appendix 2 – Schedule of Procedures

ACTIVITY	**Pre-study**	**Visit/contact 1**	**Follow up, day 5 after DPC**
Patient identification (initial triage with liaison with respective clinical team/s)	x		
Informed consent		x	
Risk stratification		x**	
Direct oral Penicillin Challenge (DPC) for 'low risk' patients		x	
Follow up of patient on day 5 (or sooner if needed)			x
Counsel patient regarding initial outcome of DPC		x	
Counsel patient regarding final outcome of DPC			x
Update patient hospital records regarding penicillin allergy status			x
Written communication to GP with a copy to patient			x
Interviews with patient*			

Focus groups	[redacted]	This is independent of WS1 and WS3 and will be organised by study team during the study period considering logistic issues

**this will be conducted after DPC and will be arranged at a mutually convenient time.*

***in pre-surgical and Haematology-Oncology patients this might be done remotely prior to visit for DPC.*

10.11 Appendix 3 – Amendment History

Amendment No.	Amendment to Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	12.0	22 Jul'22		Protocol changes with reasoning: 1. Permission to contact patients directly via telephone to seek permission to forward PIL. A significant proportion of patients are undergoing remote consultations due to the pandemic. This proposed amendment will not only contribute to a more inclusive approach to participation but also enhance recruitment rate. (Page 22) 2. In the event that the recruitment targets are not met at a certain study site, other centres will aim to compensate with additional participants within respective clinical settings to achieve the proposed sample size and this will allow us to catch up for pandemic related delays that has affected the study thus far.(Page 29) 3. Patients who commence opportunistic de-labelling and then develop an intercurrent infection that requires a full therapeutic course of amoxicillin or an alternative penicillin antibiotic, will be switched to therapeutic de-labelling following discussion between research team and respective clinical teams. This amendment is likely to improve clinical outcome. (Page 25) 4. A paper copy or an electronic copy of the duly signed consent form will be forwarded by the research team to patient's G.P by post or electronically respectively to expedite communication to G.P.(Page 25) 5. Acute Medical Unit: the pandemic has forced local changes at trust with some acute medical patients being admitted to other wards. The proposed amendment will enable research teams to reach out to

				patients admitted on these wards. Study protocol per se will not be compromised.(Page 10, 20, 32, 41) 7. Permission to forward DPC letter via secure email where possible to expedite communication to G.P (page 25) 8. Time to consent for AMU/ID patients: We propose to obtain informed consent within an hour following issue of PIL in low risk patients where the clinical team has identified a need to treat with a penicillin antibiotic. A similar approach will also apply to those patients who clearly demonstrate an understanding of the DPC procedure and are willing to provide informed consent. We will ensure principles of GCP will be strictly adhered to. This approach will also align with rapid turnaround times in acute settings.(page 21) 9. Pregnancy test- There is no actual change to the selection criteria. However we have added urine pregnancy test prior to DPC as suggested by the research governance department at sponsor site (Page 24)

10.12 Appendix 4: CVs