Improving drug allergy diagnosis in surgical patients

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I confirm that the work submitted is my own, except where work which has formed part of jointly authored publications has been included. My contribution and the other authors to this work has been explicitly indicated below. I confirm that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 2: **SAPPHIRE: safe antimicrobial prophylaxis for surgery study.**

This multicentre collaboration delivered two distinct studies:

1. Examining associations between drug allergy labels and risk of surgical complications.
2. Determining risks and benefits of perioperative antimicrobial prophylaxis

I led the study inception and design, delivery and oversight of data collection, and data analysis for study 1. Dr Tom Abbott (Queen Mary University London) led the second study, the data from which will be published separately and are not presented in this thesis.

Chapter 3: **Spurious Penicillin Allergy in Secondary Care: SPACE study**

I co-led this multi-centre study with Prof Thirumala Krishna, University of Birmingham, which was funded by NIHR HS&DR (129069). I was senior author on the subsequent publication in the Journal of Infection, in March 2024 (see paper 8, page iv, below) and co-author on two additional publications which arose from this research (see papers 3 and 5, page iv, below). I co-led the funding application, inception, design, and delivery of the SPACE study across all sites, data analysis, and writing of the final report of the study for the NIHR and submitted manuscript. The study comprised three patient cohorts; in this thesis, I present the findings from the surgical patient cohort as a standalone piece of work, including a new analysis of the original data.

Chapters 4: **PASSPORT: Penicillin allergy risk stratification tool for use by non-allergists in the perioperative setting: an agreement study**

This was a two-centre study, comprising both an agreement study and process evaluation. I led the inception, design and delivery of all aspects of this work. For the agreement study, Priya Dias (Clinical Trial and Research Manager at Queen Mary University London), contributed significantly to the development of the risk stratification tool and to the delivery of the study at the Barts Trust site. In recognition of this contribution, she is first author on

the PASSPORT paper which has been accepted for publication at the time of writing (see paper 1, page iv, below). This paper also includes a summary of the findings of the process evaluation conducted within PASSPORT, which is detailed in Chapter 5 of this thesis. All aspects of this evaluation were led and delivered by me, including data analysis.

Chapter 6: **Understanding patients' perceptions, knowledge and experience of perioperative hypersensitivity reactions: a qualitative interview study.**

This was a single centre study which I designed, led and delivered, and for which I conducted the data analysis. This work was accepted for publication as a jointly authored paper in 2025 (see paper 2, page iv, below).

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3. R Bestwick, R Bhogal, K Kilonaviciute…..**L Savic……**SA Misbah, T Krishna. An Economic Evaluation of Direct Oral Penicillin Challenge for De-Labelling Low Risk Patients With a Penicillin Allergy Label. *Clinical and Experimental Allergy.* 2025. https://doi.org/10.1111/cea.14633

4. **Savic L**, Silverside J, Leslie K. Sugammadex Anaphylaxis: Mechanisms, Diagnosis and Incidence. *Anaesthesiology*. 2025 http://doi.10.1097/aln.0000000000005431

5. JH Yogini, I Williams, M McErlean…….**L Savic**, T Krishna. Factors influencing implementation and adoption of direct oral penicillin challenge for allergy delabelling: a qualitative evaluation. *BMJ Open Quality.* 2024. https://doi.org/10.1136/bmjoq-2024-002890

6. A Littlejohns, **L Savic.** Management and treatment of perioperative hypersensitivity. *Current Opinion in Allergy and Clinical Immunology.* 2024. https://doi.org/10.1097/aci.0000000000001000

7. A Dodd, PJ Turner, J Soar, **L Savic.** Emergency treatment of peri-operative anaphylaxis: Resuscitation Council UK algorithm for anaesthetists. *Anaesthesia.* 2024. https://doi.org/10.1111/anae.16206

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Implications for healthcare systems. *Journal of Infection.* 2024. https://doi.org/10.1016/j.jinf.2024.01.015

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13. **L Savic**, M Arden-Jones, A Avery…….A Warner. BSACI guideline for the set-up of penicillin allergy de-labelling services by non-allergists working in a hospital setting. Clinical and Experimental Allergy. 2022. https://doi.org/10.1111/cea.14217

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Abstract

Life-threatening allergic reactions to drugs can occur in any patient undergoing surgery and anaesthesia. The patient perspective on these events and their implications for future surgical safety, are unknown. In parallel with this problem, an estimated 1.5 million NHS surgical patients each year carry a label of drug allergy. These problems are interdependent, since fear of genuine allergy drives the precautionary approach to allergy labelling. Most drug allergy labels are incorrect. Nevertheless, their presence leads to avoidance of important drugs in the perioperative period, the impact of which is largely unknown. A critical shortage of allergy specialists means that allergy testing is largely inaccessible. For patients labelled 'penicillin allergic', recent research has focussed on widening access to testing through provision by non-allergist healthcare professionals. However, the evidence supporting this approach is unreliable.

The overarching aim of my research was to understand the scale and nature of any associations between drug allergy labels and post-operative complications, to determine safety and effectiveness of non-allergist penicillin allergy testing in surgical patients, and to understand patient attitudes and behaviours following a suspected perioperative allergic reaction.

I determined that the presence of a drug allergy label was associated with a 20% increase in the risk of post-operative complications, predominantly driven by infective complications among patients with antimicrobial allergy labels. I also demonstrated that non-allergist penicillin allergy testing is likely to be both clinically ineffective and unsafe. Lastly, I identified that patients who suffer suspected perioperative allergic reactions can experience life-limiting anxiety and may struggle to recall their allergy diagnosis, increasing their risk of future reactions.

Future research must focus on developing safe, effective pathways for pre-operative drug allergy delabelling to reduce the burden of surgical complications, and improving safety of future surgery among patients who suffer perioperative allergic reactions.

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1 Introduction

1.1 The clinical problem addressed in this thesis

Drug allergy is a critically under-researched problem in the surgical population. More than a quarter of UK surgical patients carry an unsubstantiated label of allergy to one or more drugs, frequently drugs which are important for safe and effective surgical care such as antibiotics and analgesics (1). These labels are usually incorrect, applied when side effects are misattributed to allergy by the patient or their healthcare provider (1). The impact of such labels is not completely understood, but previous work suggests that rather than improving patient safety, avoidance of the suspected causal drug and the use of less effective alternatives, can lead to increased complications and poor health outcomes (2-4). Our current healthcare systems lack the capacity to test and remove incorrect allergy labels prior to surgery, resulting in a large burden of potentially avoidable harm (5).

In addition to incorrect allergy labelling, patients undergoing surgery and anaesthesia are at risk of genuine hypersensitivity reactions to drugs administered in the perioperative period (6). These reactions are often severe and life-threatening. Survivors may require intensive care admission, and can suffer long-term renal and cardiac impairment as well as post-traumatic stress disorder (7). Our understanding of the incidence, causes and outcomes of perioperative reactions is hampered by variation in the investigation, reporting and case definition for these events. Furthermore, limitations in the diagnostic accuracy of routinely available tests can make it difficult to confidently identify a culprit drug, leading to diagnostic uncertainty for half of the patients investigated (unpublished data from the Yorkshire Anaesthetic Allergy Clinic). This uncertainty leads to the precautionary avoidance of multiple drugs, many of which are essential for safe and effective surgical care. This can limit or even preclude future surgery (6, 8, 9). If an incorrect diagnosis is made, patients are at risk of being re-exposure to a drug which they are genuinely allergic to – resulting in further life-threatening reactions. In addition to these problems, there is increasing appreciation of the potential mental health impact of suspected perioperative allergic reactions, but detailed research on attitudes, knowledge and perceptions is currently lacking (7).

The UK surgical population is increasing in age, comorbidity and complexity (10) . Meanwhile, the prevalence of drug allergy labelling and incidence of perioperative hypersensitivity reactions also appears to be increasing and may lead to poorer health outcomes for patients. Despite this, there is little research into the impact of drug allergy on this population or ways to improve diagnostic pathways in drug allergy. Better management of drug allergy is likely to drive incremental improvements in the safety and effectiveness of surgical care, producing both individual and societal benefits. With an estimated 7.8m patients waiting for surgery in the UK at the time of writing, the need for these improvements has never been greater (11).

In the following introductory sections, I will first describe the terminology, pathophysiology and underlying mechanisms, and clinical manifestation of drug allergy, as well as the principles of investigation. I will then outline the key issues around incorrect drug allergy labelling and perioperative hypersensitivity reactions, and describe the unmet research needs for each of these.

1.2 Terminology and classification in drug allergy

Nomenclature when describing drug allergy is variable, inconsistent and often unhelpful. The terms allergy, hypersensitivity and anaphylaxis are often used interchangeably, but do not mean precisely the same thing. Various international statements have been published which define and delineate terms, but despite these efforts to standardise terminology, persistent variation remains a significant problem (12-14).

The term ‘allergy’ describes a specific pathophysiological process involving the adaptive immune system (typically involving IgE antibodies, although IgG-mediated pathways may also contribute) and resulting in characteristic signs and symptoms. Hypersensitivity is broader term, used to describe idiosyncratic drug reactions with identical clinical features to allergy, but caused by different pathophysiological mechanisms. This encompasses reactions caused by both innate and adaptive immunity, which are typically mediated by the same effector cells and vasoactive substances. However, it also encompasses reactions caused by entirely different mechanisms and/or effector pathways. Throughout this thesis I will use the term hypersensitivity, to reflect this broad range of underlying biological mechanisms.

Anaphylaxis is simply the clinical term used when a hypersensitivity results in a reaction which is severe or life-threatening. The term is loosely translated from Greek as the opposite of prophylaxis (protection) and is agnostic to the underlying mechanism.

1.2.1 Classification systems

The original Gell and Coombs classification of hypersensitivity reactions, developed in 1963, categorises hypersensitivity into four types:

1) immediate, IgE-mediated

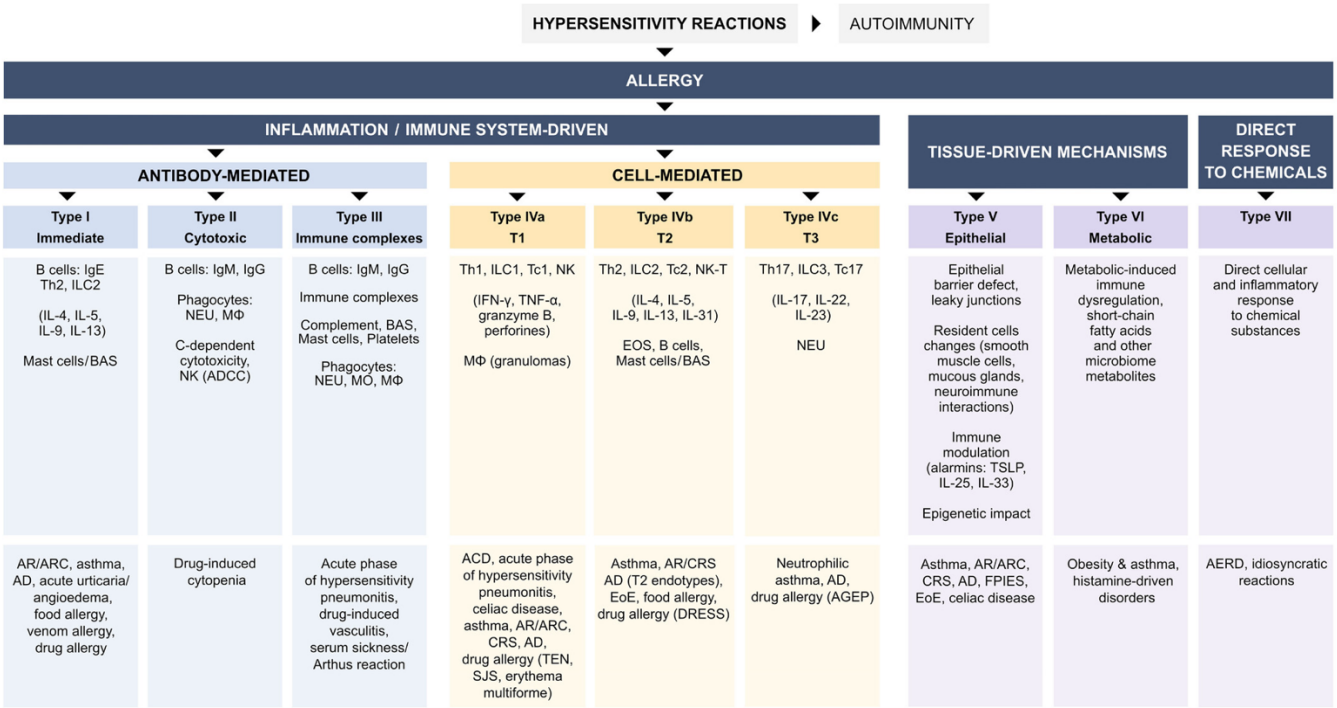
2) cytotoxic, IgG/M mediated

3) IgG/M immune complex-mediated

4) delayed, T-cell mediated.

Since then, revisions and updates have been added to this classification, in recognition of our expanded understanding of pathophysiological mechanisms. In 2023, the European Association of Allergy and Clinical Immunology (EAACI) published a more complete classification, which included seven categories broadly divided into antibody-mediated reactions, cell-mediated reactions, tissue-driven reactions and direct responses to chemicals (13). See Figure 1 below for this update classification.

Figure 1: Nomenclature of allergic diseases and hypersensitivity



Source: Updated nomenclature of allergic diseases and hypersensitivity from the European Academy of Allergy and Clinical Immunology (M Jutel et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy, 2023)

The pathophysiology and clinical features of cytotoxic cell-mediated reactions, immune complex-mediated, or cell-mediated reactions are not described in any further detail in this thesis, the main focus of which is on immediate hypersensitivity.

1.3 Clinical manifestation of drug hypersensitivity

1.3.1 Immediate drug hypersensitivity reactions

This definition encompasses Type I, IgE antibody-mediated reactions (allergic reactions) as well as other, immediate hypersensitivity pathways such as activation of the MRGPRX2 receptor or disruption of the COX-1 enzyme pathway (non-allergic reactions). See section 1.4:

Pathophysiology of hypersensitivity reactions for further mechanistic detail. Immediate hypersensitivity reactions are the main focus of my thesis.

Immediate reactions are typically defined as those occurring within one hour of exposure to the drug in question, although reactions may still be considered as immediate if they occur within 6 hours. Reactions most often occur on exposure to the first exposure of a new course of the drug. Signs and symptoms can be divided into cardiovascular, respiratory, cutaneous, gastrointestinal, and neurological. See Figure 2 for summary of signs and symptoms which may be experienced in an awake patient, and section 1.7 for a more detailed description of observable signs in the perioperative setting.

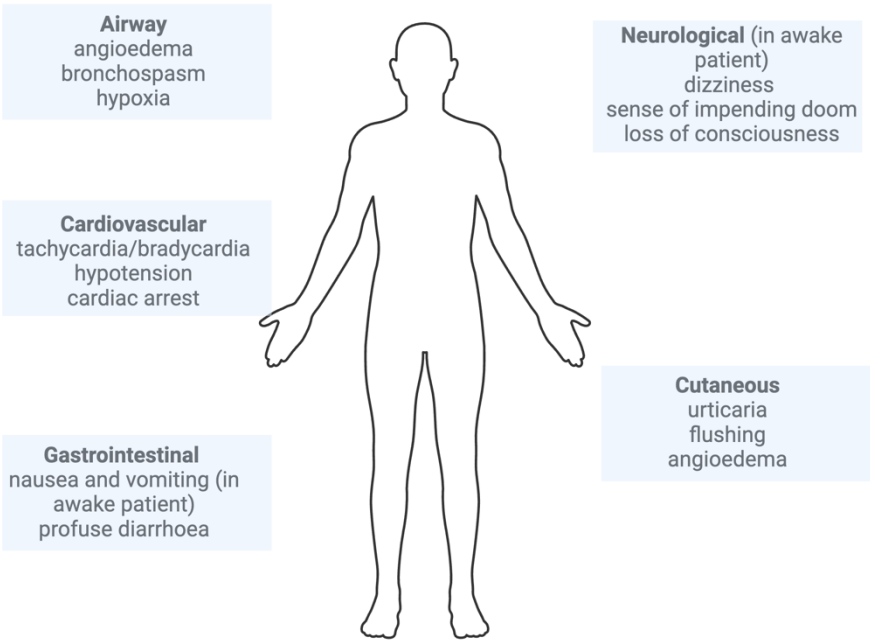


Figure 2: Signs and symptoms of hypersensitivity and anaphylaxis in awake patient (created using BioRender)

1.3.2 Non-immediate hypersensitivity reactions

These are defined as reactions occurring more than one hour after exposure to the drug in question, commonly several days or even weeks after treatment. Maculopapular exanthemas

and delayed urticaria are the most common presenting signs for this group of reactions. However, more serious reactions can occur such as including toxic epidermal necrolysis (TENS), and acute generalised exanthematous pustulosis (AGEP), and the cutaneous features can be accompanied by systemic features, such as with DRESS reactions (drug rash with eosinophilia and systemic symptoms. Non-immediate reactions are predominantly T cell-mediated (see sections below for further mechanistic detail).

1.4 Pathophysiology of immediate hypersensitivity

1.4.1 Allergic hypersensitivity reactions

Allergic reactions are the result of dysfunction of the adaptive (learned) immune system. This system is designed to protect the host from infection and cancer, but can also produce inappropriate responses to substances (termed allergens) which are not normally harmful. Common allergens include pollen, food, insect venom, animal dander, and prescribed drugs (5, 15).

The underlying mechanism of such reactions is the formation of IgE class antibodies by B cells, a type of lymphocyte, in response to exposure to an allergen. The antibodies produced in this way coat the membrane of mast cells and basophils which, on re-exposure to the allergen, are then activated to release the contents of pre-formed granules (16). These contain effector mediators including histamine, leukotrienes, prostaglandins and cytokines and proteases (including tryptase in mast cells). These mediators, collectively, result in increased vascular permeability, smooth muscle contraction, platelet aggregation, bronchial muscle secretion and complement activation, leading to the signs and symptoms of allergy (see Figures 2 and 3). (6, 17, 18). In addition to IgE-mediated pathways, allergic mechanisms involving IgG class antibodies have been purported for some drugs (19). This remains unproven in in-vivo human models.

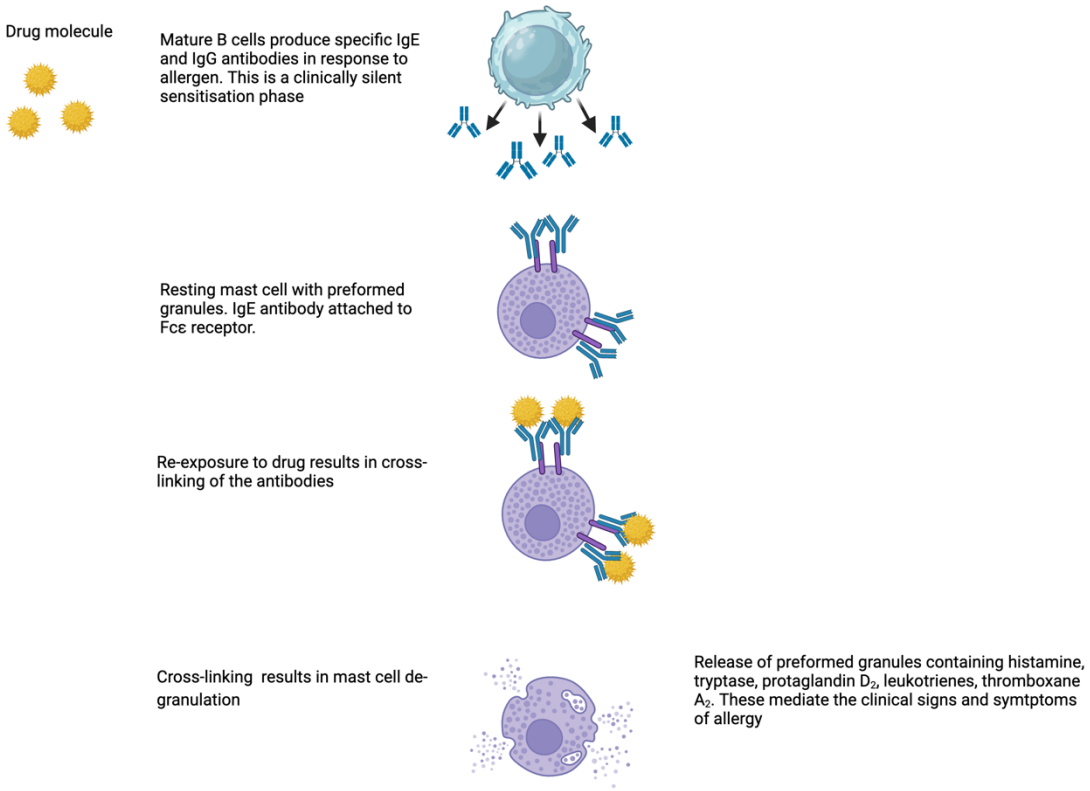


Figure 3: Pathophysiology of IgE-mediated hypersensitivity

(created using BioRender).

1.4.2 Non-allergic hypersensitivity reactions

In addition to IgE-mediated processes, there are several other pathways through which hypersensitivity reactions to drugs can occur (6, 14, 20, 21). These are summarised in Figure 4. Some hypersensitivity reactions are thought to be the result of complement activation, where cleavage of complement results in the production of anaphylatoxins C3a and C5a which bind specific G-protein coupled receptors on mast cells, basophils, granulocytes and macrophages and lead to their degranulation. This is termed complement-activation related pseudoallergy (CARPA) and has been proposed as the underlying mechanism for reactions to monoclonal antibodies, liposome-encapsulated drugs (eg doxorubicin), micellarised anti-cancer drugs (eg paclitaxel), and radiocontrast media (22, 23). Non-specific hypersensitivity can also result from interference with enzyme pathways. This includes the inhibition of the COX-1 enzyme by non-steroidal anti-inflammatory family, leading to reduced prostaglandin

synthesis, increased leukotriene production and resultant inflammatory responses most commonly characterised by urticaria and angioedema (24, 25). Another example of enzyme related hypersensitivity is the disruption of the kinin-kallikrein system by ACE inhibitors, leading to reduced degradation of bradykinin, increased release of substance P, and resultant vasodilation and fluid extravasation into the tissues causing angioedema (14, 26, 27).

In addition to these mechanisms, direct activation of mast cells and basophils is thought to occur through innate immune responses including the off-target occupancy of cell membrane receptors such as the Mas-related G protein receptor X2 (MRGPRX2). This receptor is expressed constitutively on mast cells and is inducibly expressed on basophils (28-32). Expression is greatest in skin and fat mast cells, with variable and low expression in gut and lung mast cells (33, 34). The evidence supporting the role of this receptor in non-allergic hypersensitivity reactions is mostly limited to animal and ex vivo models (29-31). Nevertheless, these pathways offer a possible alternative explanation for the reactions seen in patients who have not had prior exposure to the drug and therefore no opportunity to develop sensitisation to this. This is most notably seen with the neuromuscular blocking agent (NMBAs), for which prior exposure is often absent in patients with confirmed hypersensitivity reactions (35-37). This topic will be discussed in more detail in later sections.

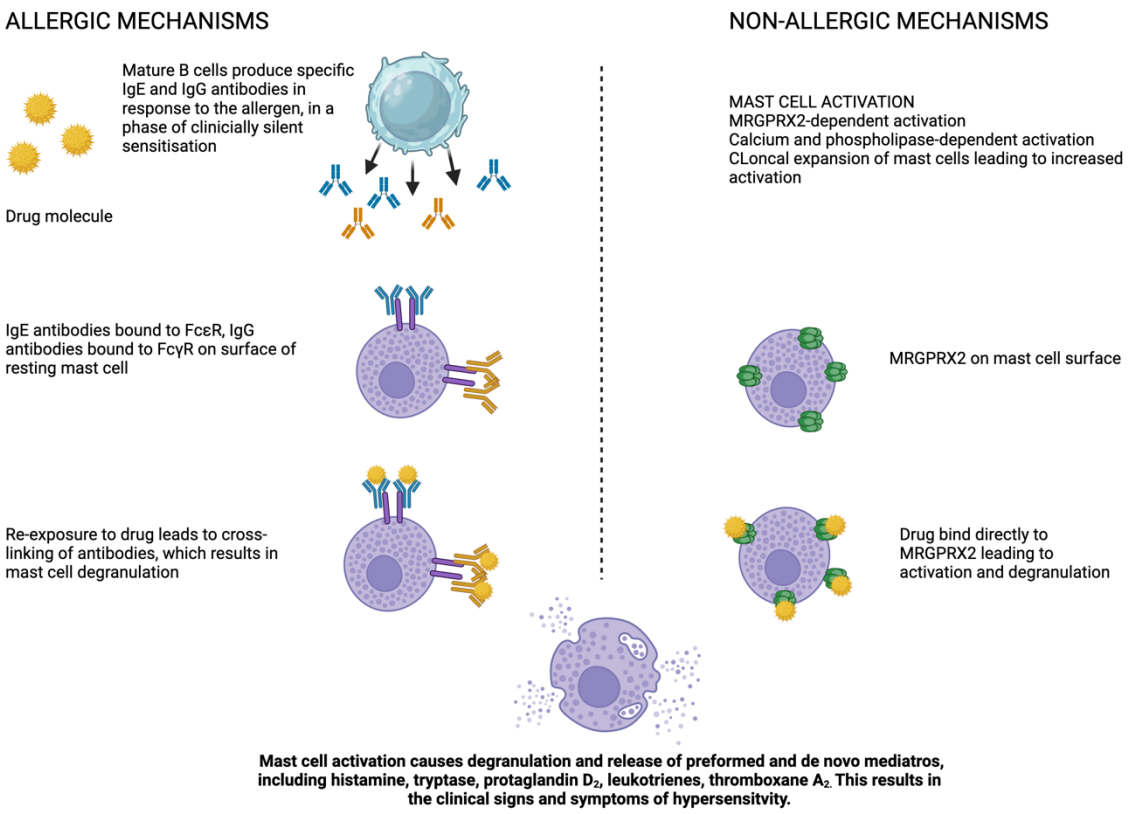


Figure 4 Mechanisms of allergic and non-allergic hypersensitivity

(created using BioRender)

1.4.3 Chemical mechanisms underpinning adaptive immune responses to drugs

Unlike food or pollen allergens which are large, complex proteins easily capable of stimulating adaptive immune responses, drugs are small molecules (typically less than 1000 Daltons) which are not thought to be recognised by the immune system. A variety of mechanisms have been proposed for how drugs elicit adaptive immune responses, including the hapten, pharmacological interaction (Pi), and altered repertoire theories.

The hapten theory postulates that drugs can act as haptens, binding covalently to a protein to create an hapten-carrier complex which then induces an immune response (38-40). Typically, the drug in question is not chemically reactive and able to form covalent bonds with proteins until it undergoes metabolism (usually in the liver) (21, 41). This theory provides an

explanation for how 'blindness' of the immune system to small molecules might be circumvented. There is evidence that this is the mechanism underpinning allergy to B-lactam antibiotics (40, 42).

Over the last two decades, an alternative mechanism has been proposed, termed 'direct pharmacological interaction of drugs with immune receptors' (Pi) theory (41, 43, 44). This states that certain drugs are capable of binding reversibly to antigen-specific receptors on T cells. Binding is thought to occur at the TCR-variable site, but this remains unproven to date. This mechanism is HLA-dependent, but independent of antigen processing and metabolism by antigen presenting cells - demonstrated by the fact that antigen presenting cells fixed with glutaraldehyde can still activate drug-specific T cell clones in the presence of soluble drug (45, 46). The lack of processing and metabolism means that T cell activation can occur within seconds of drug exposure. Evidence for the Pi mechanism comes from investigation of drug-reactive T cell clones, as well as hybridoma cells transfected with the drug-specific TCR for antigen (46, 47). This mechanism is thought to be responsible for T cell reactivity to lidocaine, atabescestat, sulphamethoxazole and carbamazepine and others.

More recently, the Pi concept has been further divided into Pi-TCR and Pi-HLA (48). In the former, the drug binds to the TCR preferentially and activates T cells through interaction with the peptide-HLA. In the latter, the drug binds the peptide binding groove of the peptide MHC, causing alteration of self peptide repertoire (the altered peptide repertoire theory). This leads to T cell activation through alloreactivity, with the altered peptide now recognised as non-self (49, 50). To date, this has only been demonstrated as a likely mechanism for abacavir, despite research into other drugs including atebescestat, a potential treatment for Alzheimer's disease (51)

Exploration of these mechanisms continues to be an active area of research, providing exciting advances in our understanding of drug allergy.

1.4.4 Risk factors for drug allergy

Risk factors can be divided into patient-related and drug-related factors. Females are consistently shown to be more likely to experience and report drug allergy, at approximately

twice the rate as males, and increasing age appears to be a risk for developing drug allergy (52-54). Certain concomitant illnesses including Epstein-Barr virus infection, SLE and HIV may predispose individuals to drug allergy, and there are also known associations between HLA type and predisposition to allergy, such as HLA-B*5701 and abacavir. For some drugs, these genetic associations may be strong enough to warrant screening prior to initiation of the drug (55). Atopy is no longer considered to be a risk factor for true drug allergy, but atopic individuals are at risk of increased severity of reactions when these occur (56).

Drug-related factors include the route of administration, with cutaneous exposure thought to be more sensitising than oral exposure, which in turn is considered less sensitising than the parenteral route. Robust data to support this are lacking. Reactions resulting from parenteral administration are typically more severe.

1.5 Investigation of suspected drug hypersensitivity reactions

1.5.1 Principles of investigation

The first and most important step in the investigation of drug allergy investigation is obtaining a detailed history of the suspected reaction (17, 57-59). This allows the likelihood of genuine allergy to be assessed and provides risk stratification which guides the planning of subsequent investigations. Key details include: the dose and route of administration; timing of the dose in relation to the reaction; signs and symptoms experienced; treatment required; and the eventual outcome. Corroborating evidence, including medical records and the results of mast cell tryptase sampling, are invaluable in this process of risk stratification. Unfortunately, the quality of information about the index event can be very limited in drug allergy, often involving historic events which are incompletely recalled and poorly documented (1, 54).

Where the diagnosis remains in doubt after assessment of the history, the definitive test to confirm or refute allergy is a drug provocation test (59, 60). This mirrors the process for food allergy testing, in which provocation testing is used to determine clinical sensitivity and/or response to treatment (61). The primary aim of this test in drug allergy should be to confirm tolerance to a drug rather than to prove allergy to it, since any allergic reaction precipitated by the test can result in a potentially harmful allergic reaction, the severity of which is difficult

to predict. To reduce the risk of precipitating a hypersensitivity reaction, patients typically undergo further risk stratification using skin tests and in vitro tests.

1.5.2 Mast cell tryptase

A key component of investigation is determining whether a rise in mast cell tryptase has occurred. ß-tryptase, a neutral serine protease, is contained within preformed granules in mast cells and is the most abundant mediator within these granules (62). When mast cells are stimulated to degranulate, tryptase is released systemically, reaching peak levels at 15-120 mins, with a half-life of 1.5-2.5 hours (62). By comparison histamine, another mediator released from mast cells, diffuses and degrades much more rapidly over a few minutes. Tryptase is therefore more convenient marker of mast cell degranulation, since the characteristic rise and fall (the so-called 'dynamic rise') in serum concentration seen in anaphylaxis can be captured with relative ease.

The upper limit for the normal range for serum tryptase concentration is generally considered to be <11.4 -15ng/ml. Elevated baseline tryptase levels are seen in a variety of conditions including mast cell clonal disorders such as mastocytosis, chronic renal disease, obesity and haematological disorders. More recently, hereditary alpha tryptasemia (HAT) has been described in the literature as a cause of raised baseline tryptase. This is an autosomal dominant genetic condition in which an increased copy number of the alpha-coding of the TPSAB1-gene leads to elevated tryptase levels. The clinical significance of the condition, which affects around 5% of the population, remains still unclear since most patients with HAT do not experience anaphylaxis or symptoms of mediator release (63).

To determine whether a significant rise in tryptase has occurred, the inflection from baseline to peak concentration (measured within the first 2 hours of a reaction) is considered more important than simply whether the peak is above upper limit of normal. The widely validated calculation to confirm a dynamic rise in tryptase in adults, is 2 + (1.2 x baseline) (64). Modifications of this calculation have been proposed for paediatric patients (65). However, the interpretation of tryptase levels is still highly context-dependent. A dynamic rise appears

to have high specificity of up to 91%, but relatively low sensitivity at 73-78%, meaning that anaphylaxis may still have occurred even in the absence of a tryptase rise (66, 67).

1.5.3 Skin testing

This involves exposing the upper dermal layer to the drug (skin prick testing), followed, if negative, by intradermal injections which are a little deeper into the skin (17, 59). See Figure 5 and 6. Positive skin tests produce a localised wheal at the injection site, but since systemic reactions are rare this is considered a very safe procedure (68). In patients with negative skin testing, the likelihood of a severe allergic reaction on drug provocation testing is low. The dilutions used for skin testing are established through determining the irritant concentration for the drug, and subsequently only using dilutions ranges below this. For many drugs, there are national or international guidelines available on appropriate dilutions, in an effort to standardise practice (57) .

Figure 5: Skin prick testing

Figure 6: Intradermal testing

(Pictures provided by Dr Linda Nel, Consultant Anaesthetist and Steering Committee Member of the UK Perioperative Allergy Network).

1.5.4 In vitro tests

These are available for some drugs and include the quantification of serum specific anti-drug IgE antibody, basophil activation testing, mast cell activation testing and the histamine release test. The presence of serum specific IgE to a drug can indicate allergy to this, and can be a useful test modality when skin testing is difficult to perform due to the patient factors detailed above (59, 67, 69).

Basophils are a key effector cell in hypersensitivity reactions (14, 70). Whole blood from patients with suspected drug allergy can be exposed (ex-vivo) to the drug in question and any subsequent basophil activation detected using flow cytometry (67, 70, 71). This may provide a functional assessment of clinical reactivity, irrespective of the underlying mechanism through which the basophils are activated.

More recently, mast cell activation testing has been developed as an alternative functional assay (72, 73). Laboratory-cultured mast cells are exposed to patient serum to allow passive

immunisation of the cells with drug specific IgE, if these antibodies are present. When the cells are exposed to the drug in question, the resulting degranulation can be detected through the use of flow cytometry (74-76) (see Figure 7) Basophil activation testing is incompletely validated and not used routinely in all centres. Mast cell activation testing is currently limited to the research domain and at the time of writing has unknown utility in the clinical setting (77).

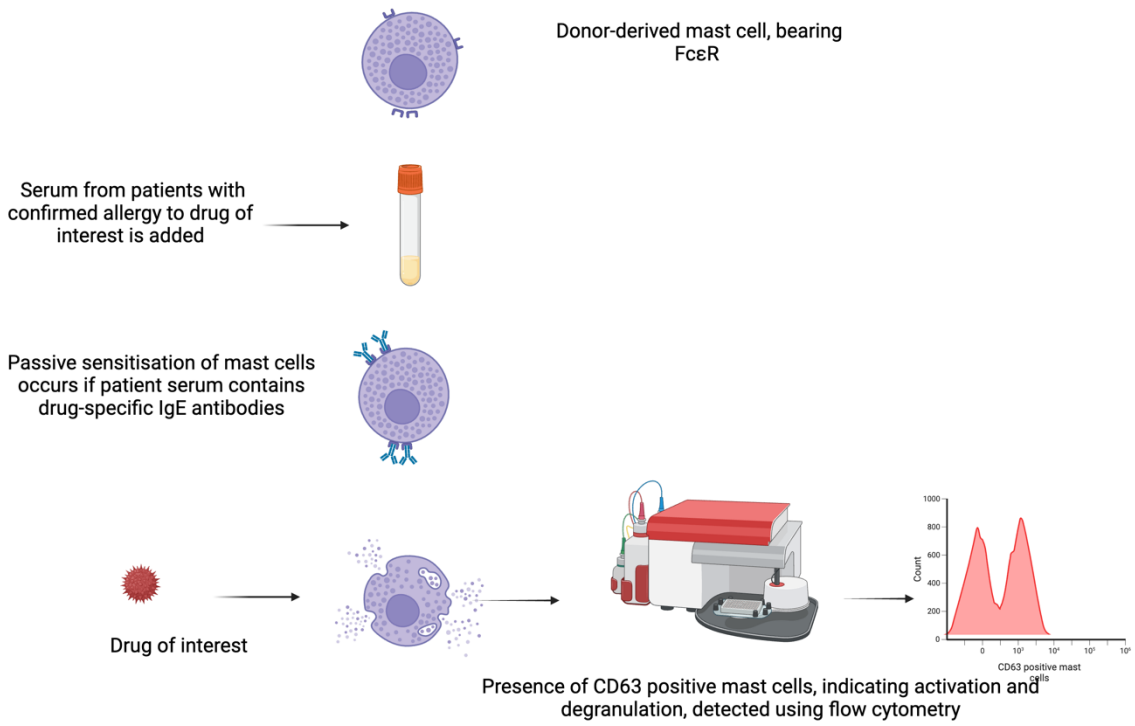


Figure 7: Schematic of mast cell activation testing (created using BioRender)

1.5.5 Limitations to skin testing and in vitro testing

There are several important limitations to the testing modalities detailed above. Skin testing can be unreliable in the presence of a variety of skin conditions, such as dermographism or extreme skin frailty, and with the concurrent use medications with antihistaminergic properties. This includes over-the-counter antihistamines, tricyclic antidepressants, and other commonly used medications. Many drugs are not suitable for skin testing due to their inherent ability to cause skin irritation in the absence of allergic sensitisation or clinical

reactivity (59, 69, 78). This includes the non-steroidal anti-inflammatory family of analgesics and morphine.

Whilst skin testing for drugs such as penicillin has reasonably well-established sensitivity and specificity, for others such as the NMBAs, these tests remain unvalidated because of the logistical difficulties in prospectively correlating skin test results to clinical reactivity through provocation testing. For new drugs coming to market, such as sugammadex (a novel reversal agent) data on appropriate skin test dilutions are even scarcer. Overall, these difficulties have led to substantial variation in the reported performance of skin testing for many drugs, particularly in the perioperative setting, and made it difficult to compare results between centres. This is discussed further in later sections.

The available in-vitro tests also have somewhat limited clinical utility (17, 69). Whilst the presence of specific IgE to a drug indicates sensitisation, the clinical significance of this is uncertain and, as discussed in later sections, sensitivity is low for many drugs (68, 69). A positive result may not predict an allergic reaction occurring on re-exposure, and a negative specific IgE to a drug does not exclude clinically relevant allergy. In the perioperative setting, an additional problem is that specific IgE assays are only routinely available for a limited number of drugs, including chlorhexidine and suxamethonium. Basophil activation testing has some utility, but is limited by the need for fresh blood samples for analysis, and the fact that 10-15% of patients have non-responsive basophils (70, 74, 77, 79). Mast cell activation testing is in its infancy in the field of drug allergy and remains unvalidated in this setting, primarily used as a research tool (72, 74-76).

1.5.6 Provocation testing

Following risk stratification, a drug provocation test might be indicated. This involves administration of the drug in a supervised setting, typically using incremental dosing, with the patient observed for signs of allergy (60, 80, 81). The primary objective of the test is generally to confirm tolerance to a drug rather than to prove allergy, and patient safety must be the overriding consideration when deciding whether to offer this test. The gold standard in provocation testing is to reproduce exactly the conditions under which the original drug was

administered, including route of administration and presence of any co-factors, but it is generally accepted that many of these elements cannot be reproduced. Procedures and protocols for provocation testing vary between drugs, as well as between centres and countries. However, there are some basic principles included in most protocols which are consistently detailed in the literature (59, 81-83). In broad outline, these include:

- Exclusion of patients in whom the index reaction to the drug was severe or life-threatening
- Exclusion of patients whose index reaction was in keeping with a severe, type 4, delayed hypersensitivity reaction (e.g. toxic epidermal necrolysis or Stevens Johnson Syndrome)
- Requirement for informed consent from the patient
- Performance of the test in a clinical area with immediate access to drugs, personnel and equipment required for the emergency treatment of an allergic reaction of any severity. Personnel must be trained in basic life support.
- Monitoring of their heart rate, blood pressure, oxygen saturations and peak flow prior to the test and during if any allergic signs or symptoms develop.

Provocation testing in the perioperative setting has a unique set of challenges and considerations and is discussed in more detail in later sections.

1.5.7 Access to drug allergy testing

In the UK, drug allergy testing is performed by allergists and immunologists working in specialist clinics. There are fewer than 140 such specialists in the UK at the time of writing, and drug allergy care is typically restricted to tertiary settings (84). This reflects a global shortage of allergy specialists, described by the World Allergy Organisation (15). The shortage of specialist services creates long wait times for testing across England and the devolved nations, currently exceeding 12 months in some areas (unpublished data). With limited and insufficient numbers of allergy/immunology training posts throughout the UK, the unmet need in this area is set to increase over time. These problems appear to be particularly acute in the devolved nations. For example, in Scotland, there are two whole-time equivalents

providing allergy care for a population of 5 million at the time of writing, despite the Royal College of Physicians (England) recommendation that services require one consultant immunologist per 500,000 population. It is estimated that 50% of the population in Scotland has no access to drug allergy services in the event of a perioperative allergic reaction (unpublished data), a significant patient safety issue which has yet to be addressed. The deficiencies in UK allergy care were detailed in the 2023 'Meeting the challenges of the National Allergy Crisis' All Party Parliamentary report (85). A shortage of allergy specialists has been identified at the global level by the World Allergy Organisation (15).

1.6 Precautionary drug allergy labelling

An estimated 2 million NHS patients undergoing surgery every year carry at least one drug allergy label (1). Of these, approximately 70% are not allergic to the drug(s), but may have simply experienced side-effects which were misinterpreted as allergy by the patient or a healthcare professional (18). Allergy labels are sometimes applied because a family member is thought to be allergic to the drug, even though the patient may never have received it. This sort of 'precautionary' labelling is driven by the fear of life-threatening allergic reactions; as the culture of safety in healthcare has evolved, an excessively cautious approach has resulted in the widespread over-diagnosis of drug allergy and an epidemic of unsubstantiated allergy labels (5). The labels oblige healthcare professionals to use alternative drugs which might be less effective and potentially more toxic (2, 4). There is an increasing body of evidence suggesting that surgical patients labelled with drug allergies may receive sub-optimal perioperative care, leading to worse outcomes (3, 86-88). However, a critical shortage of allergy specialists in the UK and most other countries, makes allergy testing inaccessible to most patients (15, 89-91).

In the following section, I will outline the epidemiology of drug allergy labels, and the risk factors for developing drug allergy. Using penicillin allergy as the exemplar, I will detail the impact drug allergy labels can have on health outcomes, the barriers to allergy testing, and the development of novel approaches to address these.

1.6.1 Epidemiology of drug allergy labels

Unsubstantiated drug allergy labels are common across all patient groups, in all countries, and are a growing global public health concern (15). The true prevalence is unknown. Longitudinal studies are scarce, and estimates vary widely. It is important to note that much of the published work describes the epidemiology of adverse drug reactions, rather than clinician-confirmed allergy. A population study of drug allergy in Hong Kong in 2024 examined 7.3 million individuals and determined a prevalence of 5.6% and incidence of 277/100,000 of drug allergy labels, whilst a prevalence study in the US across 20 years found that 36% of patients reported at least one drug allergy (53, 54). Data relating specifically to hospitalised patients, describe a prevalence ranging from 1.8-4.2/1000 patients, whilst studies in surgical populations have noted a prevalence of 13-29% (52, 92-94).

The most common groups of causal drugs in patient-reported allergy are antibiotics, analgesics and anticonvulsants, although reactions to radiocontrast media and other drugs are also frequently reported (15, 52, 54, 95). Penicillin is consistently the most commonly reported drug allergy. Data from an observational study of 21,224 NHS surgical patients, which I led in 2018 (DALES study) found that 29% patients reported at least one drug allergy label, most commonly antibiotics or analgesics, with penicillin the single most prevalent label, reported by 12% of patients (92).

1.6.2 Penicillin allergy as the exemplar drug allergy label

1.6.2.1 Epidemiology of penicillin allergy labelling

As detailed above, penicillin allergy is the single most frequently reported drug allergy throughout the published literature, with estimates ranging from 3 – 12% (96, 97). The majority of reported allergies are in fact adverse reactions caused by recognised side effects of penicillin, symptoms of the concomitant illness, or other unrelated and non-allergic phenomenon which occurred whilst taking the antibiotic. Concern about a possible hereditary vulnerability to penicillin allergy means that many patients report being allergic to it simply because of a family history of this. Typically, the index family member has not been proven to be allergic either, yet entire families can be precluded from penicillin use on this basis.

In the surgical population, my previous research and that of others has demonstrated a high prevalence of reported penicillin allergy, as detailed earlier. In the UK elective surgical population, 12% of patients report this label, and prevalence among patients undergoing emergency surgery is likely to be higher due to greater incidence of co-morbidity and older age in this cohort.

1.6.2.2 Health outcomes for individuals

A substantial body of evidence suggests that the label is associated with a range of poor health outcomes. These include data from population-level studies demonstrating increased risk of infection with methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* and vancomycin-resistant *Enterococcus* (VRE). One study, conducted in the UK by Blumenthal et al, found that among 64,000 'penicillin allergic' patients, the adjusted hazard ratio for MRSA was 1.69 (95%CI 1.51-1.90), and for *C.difficile* was 1.26 (95%CI 1,12-1.40) (2). In this study, increased use of alternative antibiotics accounted for 55% of the increased risk of MRSA and 35% of the increased risk of *C.difficile*. Blumenthal et al also demonstrated that all-cause mortality was higher in those with the label (98). Macy et al demonstrated that among 51,000 matched patients, there was an increased risk of MRSA (14%, 95%CI 7.1%-21.6%), *C.difficile* (23.4%, 95%CI 15.6-31.7) and vancomycin-resistant *Enterococcus* (30.1%, 95% 12.5-50.4%) compared with controls (4). Another large study of more than two million general practice records in the UK identified an almost doubling of the risk of MRSA infection (RR=1.90) and an increase in death within the 12 month follow up period (RR=1.08) (97). Other groups have demonstrated longer hospital stays in penicillin allergic patients, including Macy et al who determined an additional 0.59 days longer stay (95%CI 0.47-0.71), with other groups determining an increased odds ratio for length of stay of 1.061 (95%CI 1.057-1.065) and increased stay of 1.2 days (4, 99, 100). Patients with the label are more likely to require admission to intensive care, with an adjusted odds ratio of 1.42 (95%1.21-1.67) and more likely to be readmitted to hospital following discharge (100, 101).

In the surgical population, an increased risk of surgical site infections has been demonstrated, with an adjusted odds ratio of 1.51 (95% 1.02-2.22) in patients with the label (3, 102). In the UK, surgical patients are also exposed to an additional risk from the use of teicoplanin as

alternative antimicrobial prophylaxis in penicillin allergic patients. This antibiotic, which at the time of writing is only used routinely in the UK and some centres in Australia, is used as a first-line alternative to penicillin for a wide range of surgical procedures. It was brought into routine use in response to high rates of *C.difficile* and a drive to reduce cephalosporin use in the UK. However, this antibiotic is associated with the highest risk of anaphylaxis per administration of any drug used in the perioperative period. Following a case series report of patients from Yorkshire and Manchester which I led in 2015 in which this problem was first described, the NAP6 study subsequently determined that teicoplanin is associated with a 1:6000 risk of anaphylaxis (18, 103). As in our case series, up to half of patients who experience teicoplanin anaphylaxis have received this antibiotic because of a label of penicillin allergy. To date, none of the patients seen in the Yorkshire Anaesthetic Allergy clinic have tested positive for penicillin allergy on subsequent investigation, meaning that these are avoidable episodes of anaphylaxis.

1.6.2.3 Population-level outcomes

The penicillin allergy label compromises antimicrobial stewardship, enhancing the risk of nosocomial infections such as MRSA, *C.difficile* and VRE, as detailed above. At a population level, this is a key driver for antimicrobial resistance (AMR), a major global health concern (104). AMR is thought to result in 700,000 deaths per year and it is estimated that it will result in 10 million deaths per year worldwide by 2050 (105). One of the aims of the UK government National Action Plans for tackling AMR is to substantially reduce the use of broad-spectrum antimicrobials, which mediate the development of antimicrobial resistance (106). Penicillin allergy delabelling is likely to contribute to these efforts.

The economic impact of penicillin allergy labels has also been elucidated in recent years. UK data suggest that these labels are associated with increased healthcare costs, estimated at up to $609 for direct drug costs per patient admission, as well as lower outpatient prescription costs, in a systematic review of 30 studies (107). The cost of alternative antibiotics over a lifetime has been estimated at $1900 (108). The overall costs of increased healthcare requirements from treatment failure and other harms associated with penicillin allergy have yet to be robustly determined but it is generally accepted that these will be high.

1.6.2.4 Evidence of benefit from penicillin allergy delabelling

It is important to note that much of the benefit from delabelling is presumed, rather than proven. Several studies have demonstrated an increase in the use of penicillin antibiotics and decrease in the use of broad-spectrum alternative following delabelling, as well as decreased total doses of antibiotics used (109-111). Macy et al determined that healthcare utilisation was lower over a three year follow period in patients who were delabelled vs controls, with fewer outpatient and emergency department visits and fewer days in hospital (110). The long-term impact on rates of infection with MRSA, VRE and *C.difficile,* as well as rates of treatment failure and mortality, are much harder to capture, requiring robust, population-level longitudinal studies.

Several groups have tried to define whether there is health economic benefit to be made from delabelling, using actual or modelled data on healthcare costs. Most of this work concludes that delabelling is cost saving, when accounting for the cost of the testing itself weighed against presumed reductions in antibiotic consumption, hospital bed stays, and other resources (110, 112). However, many of these models do not take into account the full cost of the delabelling pathway and are reliant on estimated cost savings in future healthcare. The SPACE study, detailed in Chapter 3, performed a comprehensive assessment of the full cost of delabelling, and found that this varied depending on the setting the testing was conducted in and the skill mix of the personnel delivering this (113).

1.6.2.5 Current and novel testing pathways for penicillin allergy

Current pathways

The current standard of care for penicillin allergy testing in the UK is detailed in the 2015 British Society of Allergy and Clinical Immunology guideline (114). This states that patients should be assessed in a specialist allergy clinic, and outlines the different approaches to management depending on whether the history is consistent with a Type 1 immediate hypersensitivity reaction, or a Type 2-4 reaction (see earlier section on Gell and Coombs classification of hypersensitivity reactions). In this section, I will focus only on the management of suspected immediate hypersensitivity. The guideline recommends that

patients are offered skin testing, without or without serum specific IgE quantification, except in cases where the 'allergy' history is that of a family history only, or the patient has received the same penicillin again uneventfully. The guideline notes that the sensitivity of specific IgE is low and that this test should only be offered in conjunction with skin testing, unless the index reaction was very severe, and skin testing is felt to be high risk. Other testing modalities such as basophil activation testing and the lymphocyte activation test were not considered to be sufficiently validated for routine clinical use. Where skin tests are negative, oral provocation testing is recommended. This test was noted to have high negative predictive value (94%), with occasional false negative results which might be the result of an absence of co-factors which lower the threshold for reaction. The guideline includes a separate management approach for children with penicillin allergy, which I will not detail here since adults are the focus of my research.

The UK approach is broadly similar to that of other countries. In Europe, a recent update to guidelines was produced following a survey of practice. These guidelines emphasise the need for careful risk stratification of the allergy history, with subsequent testing tailored to this risk profile. Adopting a cautious approach, skin testing with or without specific IgE testing are recommended for all patients, with the only group considered safe for direct provocation being patients who present with palmar exfoliative exanthema. American guidelines produced 4 years later took a slightly less risk averse approach, stating that in patients whose allergic history was of a distant, benign rash without any systemic symptoms, then a direct provocation test could be considered (81, 83).

With an estimated 6% of the population labelled as allergic to penicillin, representing nearly 3 million people, the potential burden of testing is extremely high within routine clinical care (97). Given the paucity of allergy specialists in the Uk, the National Institute for Clinical Excellence (NICE) developed a clinical guideline (CG183) which states that patients should be referred for specialist testing **only** if they:

- *need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic* ***or***
- *are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency) (58).*

Most patients with the label therefore cannot access allergy testing. Those who can often face long waiting times. This model cannot meet current or future demand, which is only set to increase as the population ages. The provision of delabelling at-scale is therefore only likely be possible with the engagement of clinicians whose primary training is not in allergy or immunology, referred to in the rest of the thesis as "non-allergists". The pathways which have been developed for use by non-allergists are outlined in the section below. Later in this thesis I describe my research into the implementation of such pathways and the potential barriers and enablers to this.

Novel pathways

Studies from the last 10 -15 years have demonstrated that patients at low risk of true penicillin allergy can be accurately identified based on their allergy history alone, and can proceed to a 'direct' provocation test without prior skin tests or in vitro tests (115-121). Indeed, the use of skin or in vitro tests in this cohort can result in false positive results, which preclude the administration of a provocation test (65). This more streamlined approach is quicker, less invasive, and less expensive, and therefore may increase the scalability of testing. Furthermore, without the need for allergy specialist input to perform and interpret skin tests and in-vitro tests, there is the potential that non-allergists could deliver the testing, which would facilitate much wider provision of delabelling within healthcare systems.

Recent work has focused on two key aspects of this approach. The first is the safety of direct provocation testing without prior skin testing. A recent systematic review of around 1200 patients tested by allergy specialists using this pathway, found that this was a safe and appropriate technique (119). The second research question is whether non-allergists can perform safe, accurate risk assessment. Multiple efficacy studies have examined this issue, each using a risk assessment (or 'clinical decision support') tool, in which a standardised set of questions aims to identify patients at low risk of genuine allergy, excluding those with high-risk histories, or with co-morbidities which would preclude drug provocation testing (116, 117, 120-122). The definition of co-morbidities which preclude provocation testing is inconsistent, but typically includes patients with severe or poorly controlled asthma, heart failure, or severe aortic stenosis.

One of these efficacy studies, which I led in 2019, examined the performance of anaesthetists and pre-assessment nursing staff in the delivery of a delabelling pathway and was the first published study among the UK surgical population (120). We were able to delabel more than one quarter of 219 screened patients with only one, self-limiting, adverse reaction. Collectively, the available literature appears to suggest that non-allergists can reliably risk stratify patients and perform direct provocation testing, with an overall incidence of adverse reactions of between 1-3.4%, none severe or life-threatening (121). This is broadly in keeping with the expected incidence of reaction to penicillin (and other antibiotic) administration in the baseline population (123, 124). In these studies, the risk stratification and delabelling was delivered by a variety of healthcare professionals including pharmacists, nurses, anaesthetists and other medical specialists, both with and without specialist oversight. In some studies, the process of risk stratification was reduced to a five-question checklist, called the PEN-FAST tool (115). Typically, a more detailed questionnaire is employed to help non-allergists perform the risk stratification.

Based on a cumulative body of evidence suggesting safety and efficacy of non-allergist delabelling, there have been calls to implement this in routine care in several countries, including the UK. This was reflected in the 2022 British Society of Allergy and Clinical Immunology decision to commission a guideline for the delivery of such services by non-allergists, which I subsequently led (125). This guideline provides a practical and governance framework for the delivery of delabelling in hospital settings by non-allergists, was approved by allergists and immunologists in the UK and further endorsed by more than 14 national stakeholders. In parallel, the International Suspected Perioperative Allergic Reactions group, ISPAR, commissioned a guideline specifically for surgical patients. I led the writing of this consensus-based guideline on best practice, applicable across all countries represented in the ISPAR group (126). This guideline states that in low-risk allergy histories, a direct provocation test can be considered.

1.6.2.6 Limitations to our understanding of the safety and effectiveness of non-allergist delabelling

There are substantial limitations to the generalisability of the current evidence base, and uncertainty remains about the safety and effectiveness of non-allergist delabelling. This is the focus of the PASSPORT study (Chapters 4 and 5) which I performed as part of this fellowship, in which I explored the diagnostic accuracy of non-allergist delabelling when using a risk assessment tool. A further limitation is the lack of detailed qualitative work exploring patient and healthcare provider perspectives on the acceptability of non-allergist delabelling. Many of the studies referenced above included data on acceptability of the pathway only among selected cohorts of patients who expressed interest in taking part in the study and being delabelled. The voice of patients who decline this testing remains largely unheard. Among healthcare professionals delivering the pathway, qualitative research suggests that whilst they understand the potential benefits of delabelling there is limited experience of referring patients for testing and uncertainty around whether patients would take penicillin following a negative test (127, 128). My experience of non-allergist delabelling has led me to believe that major barriers exist to the implementation of such pathways. This is explored further in the process evaluation embedded within the PASSPORT study, detailed in Chapter 5.

In summary, there are no definitive clinical trials to date determining the effectiveness of non-allergist delabelling or accurately describing the impact of this intervention on health outcomes. We lack detailed qualitative data exploring the barriers and enablers to the implementation of this intervention, and there are no robust health economic analyses to support its use. My fellowship aims to provide better understanding of whether this is an appropriate intervention for use in routine clinical care.

1.7 Perioperative drug allergy

In addition to the problem of pre-existing drug allergy labels in the surgical population, every patient who undergoes surgery and anaesthesia is at risk of suffering a life-threatening allergic reaction in the perioperative period. In this section, I will outline the key aspects of this problem, including the difficulty making a diagnosis in this patient group and the potential long-term impact of such events on individuals.

1.7.1 Pathophysiology of perioperative hypersensitivity reaction

As described earlier in this chapter, immediate hypersensitivity reactions have several possible underlying mechanisms. These are tabulated below and comprise both antibody-mediated and non-antibody-mediated pathways. The definitions used in this table do not take into account other mechanisms of hypersensitivity which are not typically seen in the perioperative setting, including type II cytotoxic and type III immune-complex reactions (both antibody- mediated) or cell-mediated, delayed hypersensitivity reactions. Whilst these other forms of hypersensitivity may exist, there are very few data describing incidence or severity, and they do not form part of my thesis.

Table 1: Allergic and non-allergic immediate hypersensitivity and anaphylaxis in the perioperative setting.

Term	**Definition**	**Mechanism(s)**	**Prior allergen exposure**
Allergic hypersensitivity	Specific pathophysiologic process involving the adaptive immune system	IgE-mediated IgG-mediated (limited data in humans)	Yes
Non-allergic hypersensitivity	Idiosyncratic drug reaction with identical clinical features to allergy, mediated by a variety of mechanisms	Complement-mediated through C3a and C5a MRGPRX2-mediated Cyclo-oxygenase-1 inhibition Kinin-kallikrein system Unknown mechanisms	Not necessarily
Anaphylaxis	Any hypersensitivity reactions which is severe or life-threatening	Allergic or non-allergic	Not necessarily

Adapted from Savic et al, Sugammadex anaphylaxis: Mechanisms, diagnosis and incidence. Anaesthesiology, 2025

1.7.2 Epidemiology of perioperative hypersensitivity

Reported incidences range from 1:350 to 1:20,000 patients (7-15), with mortality estimates from 1.4 to 9% (9, 16-20). Such variation in incidence may reflect geographical differences in

genetic susceptibility or drug usage patterns but is more likely to result from variation in reporting, investigation, and case definition.

Perioperative hypersensitivity is likely to be under-reported. In a study of around 5000 anaesthetics given across a large geographical area in the UK which I led in 2015, one in 353 patients had an intraoperative adverse event which met the referral criteria for allergy investigation (129). Fewer than five patients were actually referred for investigation; the reasons for non-referral of the remaining cases were not elucidated in the study. The incidence of confirmed anaphylaxis in the cohort was 1 in 2000, much higher than previous estimates.

In addition to under-reporting, variation in the investigation of patients and of case definition, limit our understanding of incidence. In some centres, every patient referred to clinic is presumed to have suffered a hypersensitivity reaction, for which a causal drug must be identified. There is an assumption that if the responsible anaesthetist thought the adverse intraoperative event was a hypersensitivity reaction, then this must be the case. Other centres do not make this assumption, and may conclude after investigation that an alternative diagnosis is more likely. For example, the relative overdose of anaesthetic induction agent causing profound hypotension, or bronchospasm due to mechanical irritation during airway manipulation (discussed further in section 1.6.3) (8, 17, 57). These differences in approach can preclude meaningful comparison between cohorts.

There is also substantial variation in the skin testing protocols used between centres, and within the same centres over time. The limited availability of 'gold standard' provocation testing for perioperative drugs (discussed later in this section) means that we are much more reliant on skin tests to make the diagnosis than is the case for drug allergy investigation in other settings. Variations in both the drug dilutions used and the definition of what constitutes a positive or negative result, can raise or lower the threshold at which sensitivity to a drug is diagnosed (57). These differences hamper meaningful comparison between centres or across different time periods, or may preclude comparison altogether. The use of in vitro tests adds further complexity. Many centres rely heavily on such tests, despite a lack of validation, whilst in other centres they are unavailable. Lastly, there is significant variation

in how groups determine denominator data for individual drug usage, adding further to the difficulty of comparing between centres. At present we are therefore unable to provide meta-analysis of pooled data within or between countries. Collectively, these limitations mean that estimates of incidence for both perioperative hypersensitivity reactions and the reaction risk for any individual drug, should be approached with a high degree of caution.

1.7.3 The pholcodine hypothesis

An important illustration for the problems detailed above is provided by the so-called pholcodine hypothesis, which states that pholcodine - an antitussive ingredient in cough mixtures - sensitises patients to the NMBA family of drugs through exposure to substituted ammonium ions which act as a shared allergenic epitope. The seminal research describing this phenomenon was a retrospective study of 650 Norwegian patients in 2005 (25, 26). High rates of NMBA allergy were observed in this country, compared to its neighbour Sweden. It was noted that a major difference between these populations was in the consumption of pholcodine, a component of many cough syrups. Withdrawal of pholcodine from the Norwegian market appeared to result in a fall in incidence of NMBA allergy in the three years after removal, compared to the prior six years. This conclusion was based on the reduction of spontaneous reporting of cases of suspected perioperative anaphylaxis. However, the nature of the reporting system used in this study meant there were no data on the results of allergy testing. It therefore remains unknown whether the reported cases were indeed genuine perioperative hypersensitivity and what the responsible drug for this might be if so. Other explanations for their data include a decreased overall incidence of hypersensitivity due to changes in drug usage patterns (for example, the use of suxamethonium fell significantly during the nine-year study period), or simple reporting fatigue during the study. More recently, the French ALPHO study reported a four-fold increased risk of NMBA allergy in pholcodine users compared with non-users (130). This was a case-control study in which 167 cases of perioperative hypersensitivity due to NMBA, were matched to 344 patients who had undergone uneventful surgery during which an NMBA was used. A history of pholcodine use in the previous 12 months was sought in both groups. There were important differences between the groups in terms of atopy and obesity, and the logistic regression models used to

select predictor variables were based on the assumption that variables were independent of each other. However, pholcodine use is associated with both obesity and atopy, due to the greater likelihood of cough in these conditions. The study was also subject to recall bias, with patients asked to remember if (and when) they had used specific cough syrups in the previous 12 months. Lastly, a six-fold increased risk of NMBA allergy was observed in patients with occupational exposure to quaternary ammonium ions, the proposed allergenic epitope in NMBA allergy. The methodological limitations to these studies should have prevented any causal inference, yet pholcodine was subsequently withdrawn from use globally, based largely on these data (131-133)

It is unlikely we will ever determine conclusively the role of pholcodine in development of sensitisation to NMBAs. Nevertheless, the evolution of the pholcodine hypothesis serves as a useful illustration of the complexities inherent to the investigation of perioperative hypersensitivity, and our limited understanding of the epidemiology of this problem.

1.7.4 Presentation and recognition of perioperative hypersensitivity reactions

Perioperative hypersensitivity can present with a wide range of single or multisystem signs and symptoms, on a spectrum from mild to catastrophic. Most reactions occur at induction of anaesthesia but can also occur at any time during surgery or the early post-operative period. Common presenting signs include hypotension, tachycardia or bradycardia, bronchospasm, urticaria and angioedema (6, 17, 64). Reactions are graded by their clinical severity using the modified Ring and Mesmer classification (see Table 2). Perioperative allergic reactions are typically more severe and quicker onset than reactions due to food or other allergens, in part because many of the drugs are administered intravenously and in relatively large doses (18). A proportion of allergic reactions present as cardiac arrest at the time of drug administration (18).

Table 2. Modified Ring and Mesmer grading scale of suspected hypersensitivity reactions

Grade	Clinical signs
1	*Skin, mucosal signs, or both:* generalised erythema, extensive urticaria, or both with or without angioedema
2	*Moderate multi-organ involvement:* skin, mucosal signs, or both with or without moderate hypotension, tachycardia, moderate bronchospasm or gastrointestinal symptoms
3	*Life-threatening mono- or multi-organ involvement:* life-threatening hypotension, tachycardia, or bradycardia with or without cardiac arrhythmia, severe bronchospasm, skin, mucosal signs, or both, or gastrointestinal symptoms
4	*Cardiac or respiratory arrest*

The signs and symptoms of hypersensitivity can be consistent with a wide range of differential diagnoses, see Table 3 below. This can hamper recognition of the event as a hypersensitivity reaction. In addition, patients are typically asleep at the time of the event and therefore early symptoms of allergy, such as itch, a sensation of impending doom, or neurological impairment are generally absent. Skin signs can easily be overlooked due to surgical drapes which obscure the patient and may not be visible to the anaesthetist until the surgery is completed, and drapes removed.

Table 3. Differential diagnoses for perioperative hypersensitivity.

Clinical symptom or sign	Differential diagnoses
Isolated hypotension without tryptase increase	• relative overdose of anaesthetic agents • vasodilatory effect of neuraxial blockade • bone cement implantation syndrome • pulmonary or amniotic fluid embolism • treatments with tricyclic antidepressants • uncontrolled bleeding • other types of shock
Isolated bronchospasm without tryptase increase	• undiagnosed or uncontrolled airway disease • airway hyperreactivity (predisposing factors such as asthma, smoking, or viral infection) • inadequate depth of anaesthesia • tracheal tube malposition • aspiration
Isolated angioedema or pharyngeal/laryngeal angioedema without tryptase increase:	• soft tissue swelling/oedema from airway manipulation • angiotensin-converting enzyme inhibitor elicited angioedema (onset 1–8 h after surgery) • inherited or acquired angioedema
Isolated skin symptoms or combined skin symptoms, hypotension and tachycardia without tryptase increase:	• non-specific histamine release • exacerbation of existing chronic urticaria/angioedema • relative overdose of oxytocin • mesenteric traction syndrome
Others	• Clonal or non-clonal mast cell disorders

Adapted from Garvey et al, Management of suspected immediate perioperative allergic reactions: an international overview and consensus recommendations. British Journal of Anaesthesia, 2019.

1.7.5 Treatment of suspected perioperative allergy

The key to successful treatment is the early use of adrenaline and fluids, alongside removal of the potential causal drugs where possible (6, 17). The immediate management of perioperative hypersensitivity was recently detailed in a consensus guideline from the International Suspected Perioperative Hypersensitivity Reactions groups (ISPAR) (8). A key difference in the management of perioperative reactions as opposed to management in other settings, is the use of intravenous adrenaline. This approach represents a more effective treatment than intramuscular use, and is the more appropriate approach when patients are under the immediate care of an anaesthetist and are fully monitored (134). In 2023 I led the development of a joint guideline from the Resuscitation Council UK, Association of Anaesthetists and Royal College of Anaesthetists on management of hypersensitivity in the perioperative setting, in which the use of intravenous adrenaline in small, incremental doses is emphasised (135). See Figure 8. Large volume and rapid fluid administration is also central to resuscitation efforts, with adults recommended to receive at least 500-1000mls or more in severe cases. Second line vasopressors and bronchodilators may be required to resuscitate the patient, particularly in treatment-resistant cases. Many patients require admission to intensive care for continued resuscitation and management. Surgery is abandoned in many cases, including an estimated 10% where surgery is considered urgent or life-saving (7). The decision as to whether surgery should continue is balanced between the urgency of surgery, severity of the reaction, and the degree of ongoing physiological disturbance.

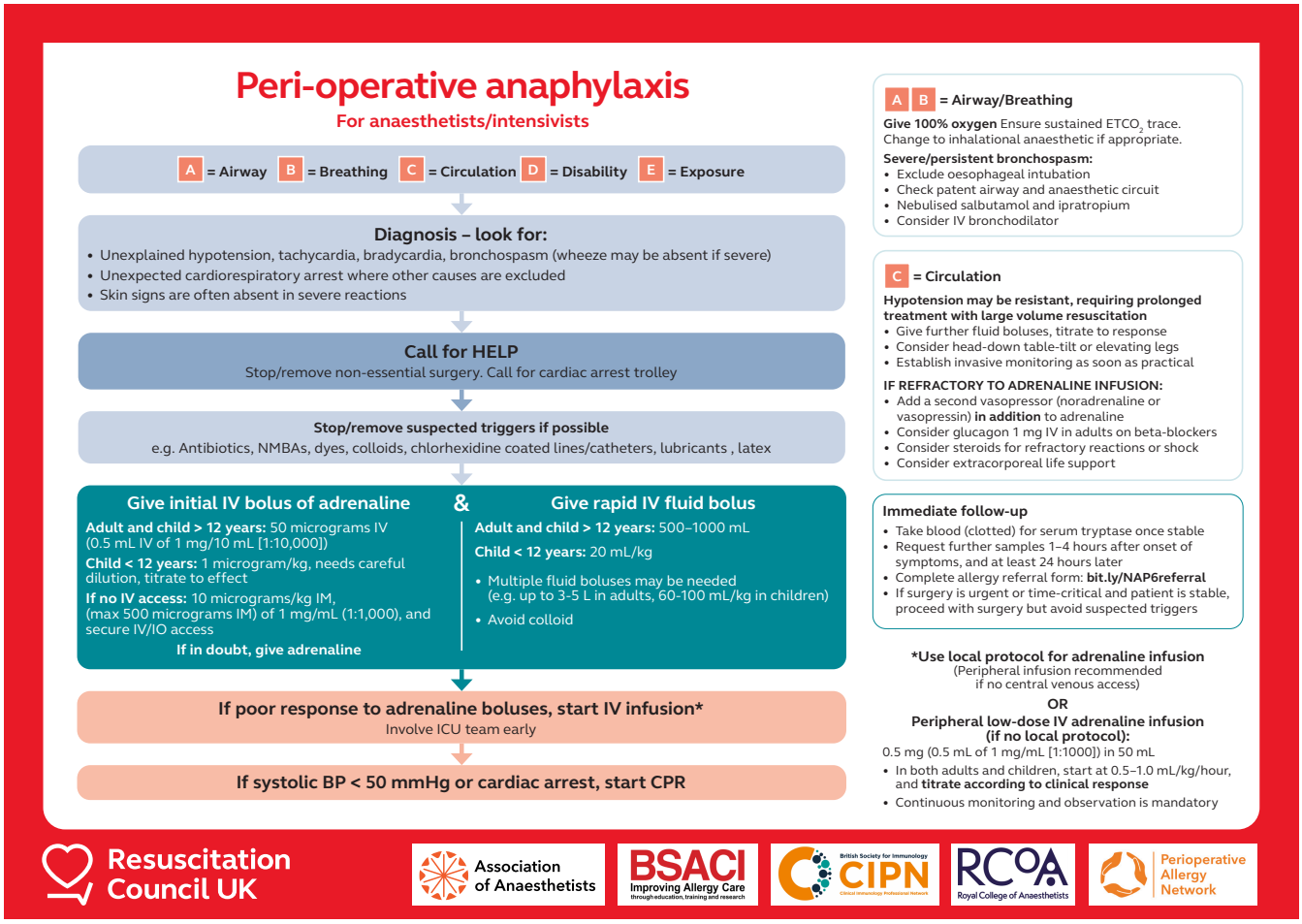


Figure 8: Treatment of perioperative anaphylaxis.

From Dodd et al, Emergency treatment of peri-operative anaphylaxis: Resuscitation Council UK algorithm for anaesthetists. Anaesthesia, 2024

1.7.6 Referral for investigation of suspected perioperative hypersensitivity

Following an episode of suspected perioperative hypersensitivity, the patient must be referred for investigation in a specialist allergy clinic. Despite national guidance detailing how to make this referral, the pathway remains obscure in many hospitals and the quality of referrals is highly variable (136). The introduction of follow-up packs containing all the relevant paperwork and blood sampling bottles in Yorkshire, which I led in 2014, substantially improved both the quality and number of referrals; this pack was later adopted by the Association of Anaesthetists as the national standard of care (137). The patient must be provided with written information detailing the suspected allergic reaction, with a list of all the drugs which must be avoided whilst awaiting investigation in allergy clinic. This is a critical

step to ensure patient safety, since patients may have limited recall of information provided verbally in the immediate post-operative period. See Figure 9 for suggested follow-up pack.

Figure 9. Yorkshire Suspected Anaesthetic Allergy Follow-Up Pack.

Contains referral form for allergy clinic, template letters for patient and GP detailing the event and which drugs to avoid pending investigation, blood sample bottles and blood forms, and a checklist for completion of the clinic referral including appropriate timings for mast cell tryptase sampling.

1.7.7 Investigation and diagnosis

1.7.7.1 Pre-test probability of perioperative hypersensitivity

The purpose of investigation is two-fold. First, to determine whether the event was indeed a perioperative hypersensitivity reaction, or whether an alternative cause for the signs and symptoms was more likely. Second, where perioperative hypersensitivity is confirmed, to identify the causal drug and a safe alternative to this for future healthcare (6, 17).

Investigation relies heavily on a comprehensive history of the index event including a clear timeline detailing the administration of drugs and onset of clinical signs. With this information, the pre-test probability of the event being a hypersensitivity reaction can be determined. This process was recently formalised by the ISPAR group, who have developed a scoring system which incorporates the clinical signs, potential confounders for these signs, and response to treatment (64, 138).

1.7.7.2 Mast cell tryptase measurement

The role of mast cell tryptase measurements is detailed earlier in this chapter. In the perioperative setting, given the range of differential diagnoses, this is arguably of even greater importance. Evidence of a dynamic rise in tryptase provides good evidence that a significant mast cell degranulating event has occurred, although as noted previously a lack of dynamic rise does not preclude this. A key limitation to the use of mast cell tryptase as a diagnostic tool in the perioperative setting is the failure of appropriate blood sampling following the suspected reaction. The provision of 'follow up packs' to simplify the process of sampling and provide clear information on sample timing, appeared to improve the proportion of patients undergoing appropriate sampling in Yorkshire (see Figure 12 above) and these packs were subsequently adopted at a national level (136, 137).

1.7.7.3 Skin testing

As detailed earlier, the cornerstone of drug allergy investigation is skin testing. However, there are additional complexities to skin testing in the perioperative setting. Several of the drugs used commonly in the perioperative setting are unsuitable or difficult to perform skin testing with due to their inherent irritant property – for example the older opioid drugs, and non-steroidal anti-inflammatories. For many others, the sensitivity and specificity of skin tests are unknown, and both false positive and negative results can occur (17, 57, 68). This is a particular problem for the neuromuscular blocking agents (NMBAs). Robust validation work is impractical for these drugs, due to the risk and complexity of performing the 'gold standard' provocation test (60, 80). For new drugs coming to market, such as the reversal agent

sugammadex, there is even less experience to guide our understanding of the performance of skin tests.

1.7.7.4 In vitro tests

Serum specific anti-drug IgE assays are routinely available in clinical practice for a limited number of drugs used in the perioperative setting – specifically suxamethonium, penicillin, chlorhexidine and latex. The specificity for these assays is generally greater than their sensitivity, but few assays have been fully validated, for the same reasons detailed above (67). For the NMBA family of drugs, many centres measure specific IgE against morphine, quaternary ammonium ions, and pholcodine, based on the underlying hypothesis that the allergenic epitope is a substituted ammonium ion common to all these compounds (139, 140). There are few robust data to support the use of these assays, and a diagnosis should not be based solely on these results (141).

Other in-vitro tests include basophil activation and mast cell activation testing, described in more detail in earlier sections. These tests provide a more functional assessment of clinical reactivity to a drug, rather than simply determining the presence of IgE antibodies, and are largely agnostic to the mechanism of cell activation. They remain unvalidated for routine clinical use in perioperative hypersensitivity and are predominantly limited to specialist centres or the research setting (17, 72, 75).

1.7.7.5 Drug provocation testing

A key limitation to accurate diagnosis in the perioperative setting is the inability to routinely perform drug provocation testing for induction agents, hypnotics and NMBAs. This sets the investigation of perioperative hypersensitivity apart from drug allergy in other contexts, where provocation testing is very widely used. The expected physiological effects of anaesthetic drugs mandate that these are only administered by an anaesthetist in a theatre setting, which presents significant logistical and other difficulties (60, 80, 142). The effects of the anaesthetic agents themselves can confound the signs and symptoms of any allergic reaction which might occur, making interpretation of these signs and symptoms more

difficult. Until very recently, these complexities have precluded the use of provocation testing, with most guidelines stating this is unethical or unachievable (59, 80).

However, without this gold standard test, patients can be left with substantial diagnostic uncertainty, resulting in the unnecessary avoidance of multiple drugs as a precautionary measure (142). This can limit or even preclude future surgery and anaesthesia. Some centres around the world, including Leeds, have developed protocols for drug provocation testing to anaesthetic drugs (60, 80) See Figure 10 for decision-making flow diagram for NMBA provocation testing. There is variation in the protocols used, with some centres favouring a full dose provocation test in which the patient is fully anaesthetised and others using a 10% maximum dose which allows the patient to stay awake (142-144). The former approach is aligned with existing drug provocation protocols whilst the latter approach reduces the complexity of the test and avoids the risks associated with administration of an anaesthetic (142). Experience remains very limited in this field, and collaborative efforts are underway to determine the ideal approach.

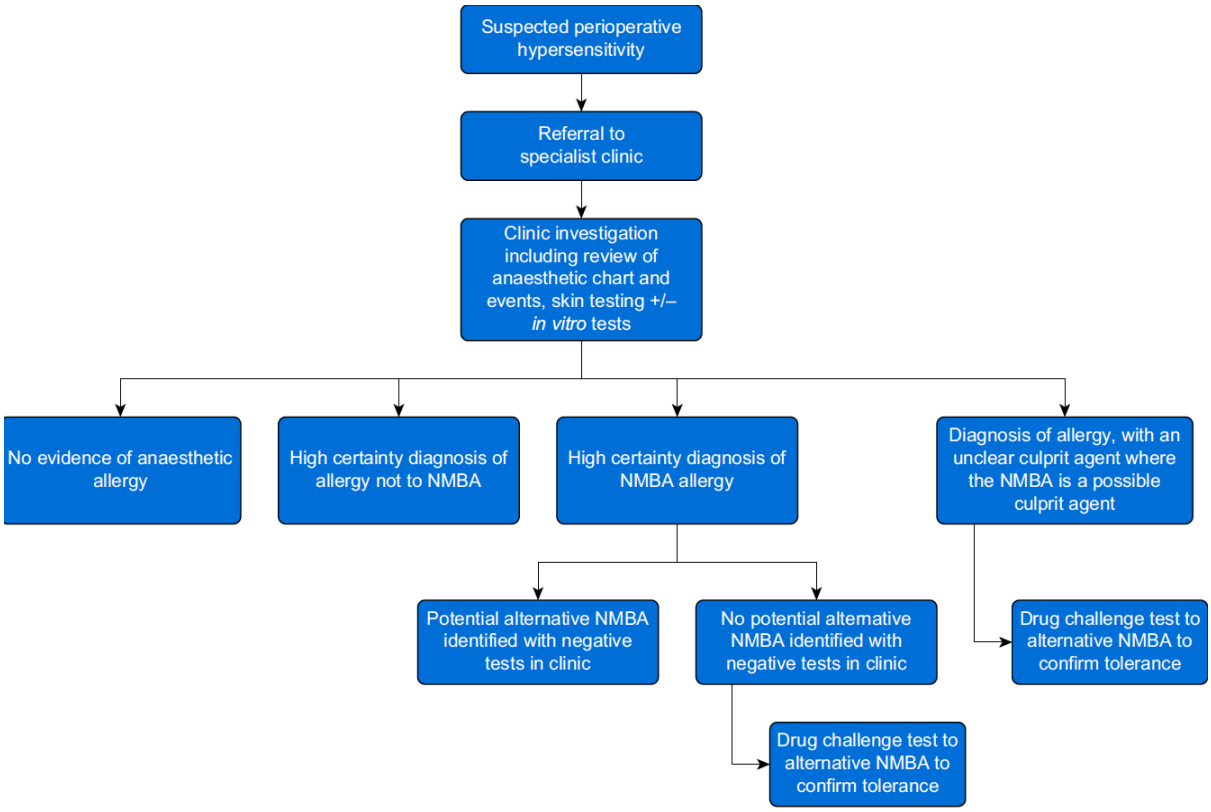


Figure 10: Flow diagram for decision making in NMBA provocation testing.

Reproduced from Savic et al, British Journal of Anaesthesia 2024

1.7.8 Causal drugs in perioperative hypersensitivity

The causes of perioperative hypersensitivity appear to vary between regions and countries. Most data are retrospective, with differing case definitions and pathways for investigation, making comparison difficult. Nevertheless, antibiotics, muscle relaxants, medical dyes, chlorhexidine and latex are typically within the top three causes (145). In the UK, antibiotics are the most frequent cause (18). Notably, teicoplanin (given as a first line alternative to patients labelled as penicillin allergic), has the highest per-dose risk of allergy for any drug administered in the perioperative period (18, 103, 146). See Table 4 in later section for breakdown of causal agents in the in Leeds Regional Anaesthetic Allergy Clinic from 2012-2025.

1.7.9 Outcomes following perioperative hypersensitivity

Mortality estimates range from 0-9% (145, 147-149). The studies contributing to this evidence base are heterogenous in nature, with widely varying case definitions and investigative pathways. Skin testing cannot be performed post-mortem and tryptase concentration can be non-specifically raised following cardiac arrest (66). Anaphylaxis is therefore a presumed, rather than proven diagnosis for most fatal cases. In the UK, an estimated 1 in 26 patients who suffer perioperative hypersensitivity will die from this reaction (7).

In NAP6, critical care admission was required for an estimated 50% of survivors of grades 3 and 4 hypersensitivity, the majority being level 3 care (18). Patients with lower grade reactions are typically unlikely to require critical care admission. Long-term health outcomes have rarely been studied in survivors, although the NAP6 study found that one third of patients suffered renal, cardiac or neurological impairment, as well as post-traumatic stress disorder (18). The economic costs of these events have not been elucidated, but include the cost of critical care admission, increased length of hospital stay, and healthcare costs associated with long-term chronic disease. In addition, there is an opportunity cost from abandoned surgery and future delays to surgery arising from the need for allergy investigation.

The impact of perioperative hypersensitivity reactions on future surgery is a key unexplored area of research. Limited work in the UK and Belgium indicates that most patients undergo uneventful surgery following specialist investigation, with an estimated 3/70 and 3/344 at the respective sites suffering a repeat perioperative event (150, 151). However, in the absence of national reporting and follow-up, these data are incomplete. Anecdotal evidence from clinicians involved in perioperative allergy suggests that patients (and their healthcare providers) may avoid future surgery because of concerns around safety. There are few or no data on the patient perspective for this clinical problem, or the impact the events have on overall wellbeing. This is a question I addressed during my fellowship, in a qualitative study conducted among patients referred to allergy clinic following suspected perioperative allergic reactions (Chapter 6).

1.7.10 Investigation, diagnosis and outcomes from the Leeds Regional Anaesthetic Allergy Clinic

1.7.10.1 Patient pathway

This is a multidisciplinary clinic which takes referrals from across Yorkshire, covering a population of around 3 million. In brief, referrals are reviewed ahead of the clinic, and if further information is required this is sought from the referring anaesthetist or other healthcare professional. Based on this information, a plan is made for which drugs will be tested and patients are contacted to ensure they are not taking any drugs with antihistaminergic properties. Where this is the case, there is liaison between the clinic, patient and GP to wean patients onto alternatives if this is deemed appropriate.

At clinic, skin prick testing is performed by a specialist nurse and the patient reviewed by the medical team. If required, intradermal is then performed. Where there is high pre-test probability of allergy to a drug and the results of skin testing align with this probability, a high certainty diagnosis can typically be made. Where results do not align with the clinical picture, a less certain diagnosis is inevitable. This can manifest in the need to recommend avoidance of multiple drugs, as a precaution. Whilst serum specific IgE quantification is occasionally used for penicillin and suxamethonium, the sensitivity for these is relatively low. A limited number of basophil activation tests have been performed for patients in this clinic, but the results of these are not used as a sole diagnostic tool due to the inherent limitations to this test, described earlier.

Greater diagnostic certainty can be achieved, as described in earlier sections, by performing a drug provocation test to confirm tolerance. Typically, this test is used in the context where a plausible culprit for the reaction has been identified, but testing is negative to the suspected culprit drug as well as other drugs given at a similar time. Alternatively, if skin testing is positive to multiple neuromuscular blocking agents (NMBAs), provocation testing might be offered to identify one safe NMBA. For induction drugs and NMBAs, provocation testing is substantially more complex to perform and carries inherently greater risk than for other drugs. The limitations to our current diagnostic tools mean that a high proportion of patients with suspected perioperative hypersensitivity receive a diagnosis which contains residual uncertainty.

1.7.10.2 Referral, investigation and outcomes

Over a 13-year period from 2012-2025, a total of 616 patients were referred to the clinic, of whom 568 attended clinic and had a complete dataset for analysis. The grade of reaction experienced by these patients is displayed in Figure 11.

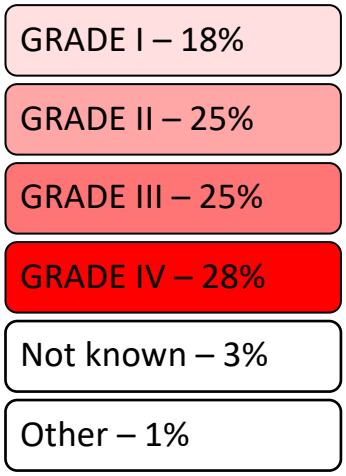


Figure 11: Grade of presenting reaction in 568 patients investigated in Leeds Regional Anaesthetic Allergy clinic

(*Unpublished data from between 2012-2025).*

Following investigation, we determined that more than one quarter (158/565) of patients had not experienced a hypersensitivity reaction, but rather a pharmacological or physiological response to surgery and anaesthesia. See Figure 12. Around 7% of patients referred to clinic did not attend. Of those with a confirmed diagnosis of hypersensitivity, antibiotics and NMBAs were the most frequent culprits, with teicoplanin the single most common cause in line with NAP6 data (18). See Table 4. For 251 patients (44% of those investigated), residual diagnostic uncertainty meant that avoidance of multiple drugs had to be recommended as a precaution.

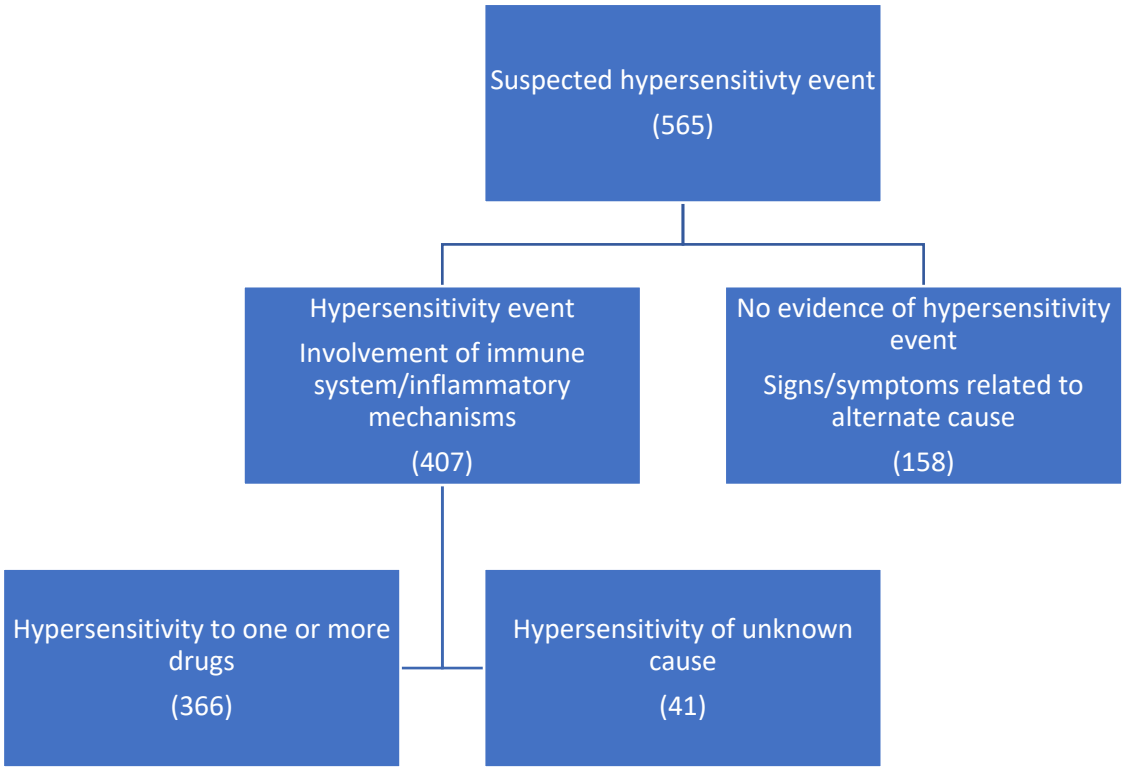


Figure 12: Diagnostic groups among investigated patients

Unpublished data from 565 patients investigated in the Leeds Anaesthetic Allergy Clinic between 2012-2025 (from a total of 617 patients referred, of whom 52 did not attend or had incomplete data).

Table 4: Breakdown of top six causal agents in Yorkshire Allergy Clinic from 2012-2025

Causal drug	**Number of cases as proportion of all patients with completed investigation (565)**
Teicoplanin	79 (14%)
Rocuronium	46 (8%)
Atracurium	54 (8%)
Patent blue	27 (5%)
Co-amoxiclav	26 (5%)
Chlorhexidine	23 (4%)

1.8 Unmet research needs in drug allergy

Surgical patients are at risk from two distinct problems related to drug allergy; incorrect allergy labelling which may impact on the safety and effectiveness of their surgical care, and rare but life-threatening hypersensitivity reactions which can occur during their surgical procedure. These problems are interdependent, with overcautious drug allergy labelling driven by the fear of genuine, severe allergy. In the following section I outline the key areas of unmet clinical and research need which will help us to improve patient care and reduce the burden of drug allergy within this population.

1.8.1 Understanding the harm associated with drug allergy labels in surgical patients

Avoidance of important drugs because of unsubstantiated concerns about allergy may lead to worse patient outcomes. The most immediate example of this is the risk of life-threatening allergy to teicoplanin when it is used in patients labelled ‘penicillin allergic’ (18). Other forms

of potential harm are only visible through large scale epidemiological studies. In other countries, increases in the risk of surgical site infection and hospital stays have been demonstrated, particularly among penicillin allergic patients (3, 102). However, these data are generally retrospective and are highly heterogenous.

The impact of drug allergy labels has not been studied in detail among the UK surgical population, and there may be important differences when comparing to other populations. These include differences in patient age, medical comorbidity and surgical complexity, as well as patterns of drug usage. An example of the latter is the UK's uniquely complex approach to surgical antimicrobial prophylaxis. Different centres recommend widely differing antimicrobial prophylactic regimes for the same procedure, typically based on very limited evidence. Outside the UK, a somewhat more consistent approach is used, with a single antibiotic (most commonly cephazolin) used for a wide range of surgical procedures (152). The UK may also differ in terms of antimicrobial resistance patterns and the use of antibiotics in the community setting. These factors can impact can affect the pattern and likelihood of infective surgical outcomes, perioperative allergy, and other outcomes.

For other common drug allergy labels, for example analgesics such as opioids, NSAIDs and local anaesthetic, the impact on patient care remains largely undescribed in the UK population. Pain results in poor patient experience and can lead to increased complications through the reduced ability to mobilise or cough post-operatively, increasing the risk of deep vein thrombosis and chest infections respectively. Detailed data describing the impact of all drug allergy labels are needed as a first step to determining which populations might benefit from pre-operative drug allergy testing and delabelling.

1.8.2 Exploring pathways for non-allergist delivered penicillin allergy delabelling

The NHS lacks the capacity to test and delabel all patients with an incorrect label of penicillin allergy. Novel pathways delivered by non-allergists may present an opportunity for provision of delabelling at-scale, in the surgical as well as other populations. Despite multiple studies demonstrating efficacy of this pathway, it has yet to be tested in a definitive clinical effectiveness trial. Key uncertainties include the diagnostic accuracy of risk stratification tools

when used by non-allergists, attitudes and perceptions of non-allergists performing the allergy testing, and the feasibility of implementing the pathway into routine care.

1.8.3 Defining diagnostic accuracy in suspected perioperative hypersensitivity reactions

A standardised approach to case definition and investigation are fundamental to the much-needed epidemiological and translational research into perioperative hypersensitivity. Such an approach would facilitate meaningful collaboration between centres and improve our understanding of the incidence, causes, and outcomes of these reactions. Whilst this is not the main focus of research within this thesis, it is an area I am actively involved in and will continue to be major research interest. This is detailed further in the concluding chapter of this thesis.

1.8.4 The patient perspective on perioperative hypersensitivity reactions

The views, attitudes and perceptions of patients who suffer these potentially catastrophic reactions are poorly understood. Anecdotal experience suggests that these events lead to substantial patient anxiety, resulting in the avoidance of future surgical care and other healthcare. Uncertainties and concern about the process of allergy testing itself may compound these issues. In order to provide effective allergy care to this population, we need to first determine the key concerns and expectations of patients following the reaction, and understand their perceptions about the diagnosis given at clinic and how this will affect their future health. Only with this richer understanding can we develop a more patient-centred approach which optimises future safety and ensures an allergy diagnosis results in more effective care.

1.9 Aims of research

My overarching ambition is to improve outcomes for surgical patients by reducing avoidable harm relating to drug allergy. In order to achieve this, my research aims to gain a comprehensive understanding of the impact of drug allergy on surgical patients, including the

impact of drug allergy labelling, as well as severe adverse perioperative events suspected to be caused by drug allergy. At a superficial level, these appear to be separate problems with entirely different aetiologies. However, they are fundamentally interdependent, because fear of allergic reactions is the motivation underpinning precautionary drug allergy labelling. Furthermore, both problems are compounded and exacerbated by the lack of access to accurate and timely drug allergy diagnosis.

In this thesis, I aim to:

1. Determine whether adult surgical patients with a drug allergy label(s) experience potentially avoidable harm from increased surgical complications, and whether these associations are stronger for particular categories of drug allergy labels.
2. Determine whether the penicillin allergy label, specifically, is associated with increased risk of post-operative complications
3. Explore the feasibility of a non-allergist delivered delabelling pathway for adult surgical patients, providing key data including the proportion of patients able to undergo this intervention in a real-world setting; the likely uptake of the intervention; and barriers and enablers to its wider NHS roll-out.
4. Explore the accuracy of non-allergist risk stratification using a tool to determine suitability for a penicillin challenge, and understand the usability and user experience of this tool
5. Understand the perspective, attitudes and behaviours of patients who experience suspected perioperative allergic reactions and allergy testing, with an emphasis on the impact of this on future healthcare interactions

1.10 Objectives of research

1.10.1 Determining associations between the presence of drug allergy labels and surgical complications

I will conduct a multicentre observational study in patients undergoing a range of commonly performed operations, in order to:

- Identify any associations between the presence of a drug allergy label(s) and the incidence of any complications within 30 days after surgery.
- Describe any associations between the number of drug allergy labels and the incidence of all surgical complications within 30 days after surgery
- Describe any relationship between presence of an antimicrobial allergy label and the incidence of infective complications within 30 days after surgery

1.10.2 Determining associations between presence of a penicillin allergy label and risk of complications

Within the cohort described above, I will examine patients labelled as penicillin allergic in order to:

- Describe any associations between the presence of a penicillin allergy label and the incidence of infective complications within 30 days after surgery
- Describe any associations between the presence of a penicillin allergy label and the number of antimicrobial agents used within 30 days after surgery

1.10.3 Determine the barriers and enablers to implementation of non-allergist delabelling in surgical patients

As part of a larger study of a non-allergist delabelling intervention, I will examine a cohort of surgical patients in order to:

- Provide descriptive data on surgical patients with penicillin allergy labels,

Provide data on feasibility outcomes for the intervention among surgical patients including uptake, reasons for exclusion, proportion of patients stratified as high and low risk, proportion of eligible, low risk patients successfully delabelled, and risk of adverse events

1.10.4 Determine the accuracy, reliability and safety of non-allergist risk stratification using a risk stratification tool

I will conduct an agreement study comparing non-allergist risk outcomes with those of allergy specialists, when using a risk stratification tool to determine suitability for a penicillin challenge test. I will:

- Determine the level of agreement and the reasons for disagreement
- Determine barriers to accurate risk stratification by non-allergists using the tool
- Provide qualitative data on user experience of the tool and how this impacts its clinical effectiveness and safety

1.10.5 Provide data on the patient experience of suspected perioperative allergy and subsequent allergy testing

Using qualitative methodology, I will:

- Develop themes which describe the range of patient perspectives, behaviours and attitudes
- Explore the potential impact of the allergy diagnosis on the patients' future healthcare interactions
- To determine how the care pathway might be improved for patients

2 SAPPHIRE: Safe Antimicrobial Prophylaxis for Surgery study

2.1.1 Background and rationale

Drug allergy labels are common in all populations and across all geographical areas, with surgical patients reporting this more frequently than other patient populations (15, 52-54, 93, 94). A UK study of more than 21,000 patients which I led in 2018, determined that 29% of elective surgical patients carry a label of allergy to one or more drugs (1). The most commonly reported allergies were antibiotics, non-steroidal anti-inflammatories and opioids, together comprising 59% of all reported allergies. These drugs are all used routinely in the perioperative period to facilitate safe and effective care. Penicillin was the single most common allergy, reported by 12% of patients. These data reflect the findings of other studies from around the world, where antibiotics and analgesics account for the majority of allergy labels and penicillin is the single most prevalent label (53, 54, 93).

There are already substantial data demonstrating that the presence of a penicillin allergy label is associated with harm, predominantly related to the receipt of broad-spectrum alternative antimicrobial therapy which leads to development of resistant organisms (2, 4, 97-100, 153, 154). For surgical patients, an increased risk of surgical site infections has been shown, as well as increased risk of anaphylaxis to teicoplanin (in the UK population) (3, 18, 102, 103, 146, 154). However, other common drug allergy labels have also been shown to impact negatively on patient health outcomes. For example, avoidance of NSAIDs has been associated with increased risk of opioid misuse in patients with chronic pain, and with increased cardiovascular and mortality risk among patients who have suffered strokes (155, 156).

The SAPPHIRE study aimed to determine the nature and extent of any associations between the presence of a drug allergy label and the risk of postoperative complications in a large UK surgical population. The findings will inform our understanding of the extent of this problem, guide future research, and help the development of effective strategies for reducing the burden of drug allergy in the surgical population.

2.2 Development of the SAPPHIRE study

At the application stage of my doctoral research fellowship, working with existing collaborators in the Critical Care and Perioperative Medicine Research Group at Queen Mary University London who have previously conducted research into antimicrobial use during surgery, it became clear that two important questions might be answered with a common dataset. The SAPPHIRE study was therefore designed to address two distinct hypotheses; first, whether the presence of drug allergy labels is associated with increased risk of post-operative complications; second, whether the benefits of prophylactic antimicrobials in surgical patients might be over-estimated, whilst their harms may be under-estimated. A dataset was designed to address both these hypotheses, creating substantial efficiencies in data collection, trial management, and delivery across multiple NHS sites.

In this thesis, I present only the work examining associations between drug allergy labels and post-operative complications. This is work I led at all stages of the study, from inception through to analysis, and which will be submitted as a standalone paper (manuscript in draft at the time of writing). I have excluded in this thesis the work examining the benefits and harms of perioperative antimicrobial use, which was led by my co-lead Dr Tom Abbott and will be published elsewhere.

The SAPPHIRE study was funded through my NIHR doctoral research fellowship (NIHR301454), supplemented by a grant awarded by the National Institute of Academic Anaesthesia for which Dr Abbott and I were co-lead applicants (WKRO-2020-0020).

2.3 Aims and objectives

The overarching aim of the study was to identify whether patients with drug allergy labels experience potentially avoidable harm from increased surgical complications, and whether these associations are stronger for particular categories of drug allergy labels. I wanted to capture the full range of the potential harms which may be associated with precautionary drug allergy labelling. My objectives were to:

- Identify any associations between the presence of a drug allergy label(s) and the incidence of surgical site infections within 30 days after surgery.

- Describe any associations between presence of a drug allergy label and the following secondary outcomes:
    - Incidence of postoperative infection within 30 days after surgery
    - Incidence of all postoperative complications within 30 days after surgery
    - Number of antimicrobial agents to prevent or treat infection
    - Incidence of antimicrobial side effects within 30 days after surgery
    - Mortality within 30 days after surgery
    - Allergic reactions within 30 days after surgery
- Describe any associations between the category of drug allergy label (penicillin allergy or non-penicillin allergy) the outcomes above.

2.4 Study design, participants and data sources

This was a multicentre, prospective observational study conducted at 21 NHS hospitals between March 2022 and October 2024, sponsored by Barts Health NHS Trust. The study was approved by the Health Research Authority and Health and Care Research Wales in February 2022 (REC reference 22/YH/0040, IRAS number 282161. See Appendix 8.11.1 for approval letter).

2.4.1 Inclusion and exclusion criteria

Inclusion criteria were adult patients undergoing one of the following surgical procedures in participating NHS hospitals:

1. Primary hip or knee replacement
2. Internal fixation of a closed long bone fracture (upper or lower limb)
3. Colorectal resection
4. Trans-urethral resection of prostate or bladder tumour
5. Caesarean section
6. Hysterectomy (vaginal or abdominal)

These procedures were selected because they are commonly performed within most hospitals in the NHS and therefore likely to provide generalisable findings. Open, robotic, laparoscopic, laparoscopically assisted and laparoscopic procedures converted to open were

all eligible versions of the above procedures. Exclusion criteria were the use of antibiotics in the two weeks prior to surgery and previous participation in the study; the former to prevent confounding from recent antibiotic use and the latter to prevent bias from repeated sampling of the same patient.

2.4.2 Exposures and outcomes

2.4.2.1 Exposures

(1) Presence of any drug allergy label

(2) Category of drug allergy label(s)

2.4.2.2 Primary outcome

All surgical site infections within 30 days after surgery

2.4.2.3 Secondary outcomes

- All infective complications within 30 days after surgery
- All postoperative complications within 30 days after surgery (see below for definition).
- Number of antimicrobial agents used from recruitment until 30 days after surgery
- Antimicrobial side effects within 30 days after surgery
- Allergic reactions within 30 days after surgery
- Death within 30 days after surgery

These outcomes were designed to capture all potential associations between the presence of drug allergy labels and negative health outcomes following surgery. The outcome of 'number of antimicrobial agents used' was selected in preference to the total number of doses, because it better describes the impact of avoiding a first-line antimicrobial. For example, if a penicillin allergy label results in the use of two different alternative antimicrobials each with only once or twice daily dosing, using the total number of doses might under-represent the true impact of the allergy label from use of multiple agents.

2.4.3 Data collection

Data were collected on all eligible patients undergoing surgery during the study period, following review of the medical notes. A standardised data set was collected for each patient recruited by the study investigators in all participating hospitals, using the data collection form (see abbreviated form in Appendix 2). Study investigators included anaesthetic trainees and consultants, medical students and research nurses. All investigators underwent training on how to complete the data collection form. Data were anonymised and entered onto a purpose-built secure internet database, which included automated checks for plausibility, consistency and completeness. There was no additional patient or primary care contact. Where data were unavailable these domains were left blank. The end of the study was defined as the 30-day follow-up for the last patient recruited into the study. Patient consent was not required as the dataset included only variables which are collected as part of routine clinical care, and no identifiable data left the hospital at which the individual was treated. At the discretion of individual hospitals, patients were screened to ensure they had not selected National Data Opt-Out, which allows patients to prevent their confidential information from being used for purposes beyond their individual care, such as for research. This occurred in Leeds Teaching Hospitals Trust in line with local information governance policies. The process in Leeds was for research nurses to screen waiting lists for potentially eligible patients, before sending the NHS number of such patients to the Information Governance team who checked whether any of the patients had opted out of data sharing for routinely collected data, so that we could exclude these patients from recruitment.

2.4.3.1 Baseline characteristics

Age was recorded as a categorical variable in ten-year epochs from the age of 18 years. Sex was recorded as male or female. The presence of any drug allergy label was recorded, and the name(s) of the implicated drug(s). Smoking status was dichotomised as current or not current smoker. American Society of Anesthesiologists Physical Status Classification was categorised as class one to four. We recorded the following chronic diseases: obesity (defined as BMI >30), liver cirrhosis, heart failure, hypertension, asthma or COPD, diabetes mellitus,

active cancer, coronary artery disease, previous stroke, or peripheral vascular disease. We defined chronic kidney disease as an estimated glomerular filtration rate (eGFR) <60 ml min^{-1} $(1.73m)^{-2}$ using creatinine measured within 30 days before surgery. The Rockwood frailty score is a 1-9 grading system describing the level of frailty experienced by patients, where a score of one indicates a very fit person who exercises regularly and is generally among the fittest for their age group, eight indicates a person who is very severely frail, and unlikely to recover from even a minor illness, and nine indicates a person who is terminally ill, without evidence of particular frailty (158). This score was used as it is a commonly applied score which can be easily learned and applied. The surgical procedures were grouped into the six categories detailed above, and investigators recorded the use of open surgical technique, whether there was wound contamination and the duration of surgery. The type and number of doses of antimicrobial drugs administered as prophylaxis and to treat a confirmed or presumed infection were recorded, including whether this was given before anaesthesia, before the start of surgery or after surgery and whether further doses were given during surgery.

2.4.3.2 Outcome data

Surgical site infections were defined according to the US CDC criteria (159). The outcome of 'all postoperative complications' is a composite of: all postoperative infections (superficial surgical site infection, deep surgical site infection, organ space infection, pneumonia, urinary tract infection, blood stream infection, intracranial infection, or infection with uncertain source), anastomotic leak, acute respiratory distress syndrome, myocardial infarction, postoperative bleed, pulmonary embolism, stroke, antimicrobial side effects (allergic reaction, acute kidney injury, diarrhoeal illness, hearing loss, tinnitus or vertigo), and death. The severity of complications was assessed using the Clavien-Dindo scale (160).

30-day follow up

A decision was made to collect data only from the hospital electronic record, rather than examining the primary care record for post-operative complications managed exclusively in

the primary care setting. This finely balanced decision weighed the importance of data completeness across all events and complications experienced post-operatively, against the substantial additional burden of requesting information from the primary care setting. Such requests are time-consuming and often not fruitful, due to the heavy demands that GPs are already under. The dataset was therefore limited to data freely available on the electronic record.

2.4.4 Statistical considerations

2.4.4.1 Sample size calculation

The incidence of complications in exposed patients was expected to be 15%, and 10% in unexposed (161). Assuming a conservative estimate of prevalence of allergy labels of 10% a sample size of 13720 patients was calculated to detect this difference with a power of 80% and significance level of 5% (two-sided test).

2.4.4.2 Statistical analyses

A statistical analysis plan was developed prior to data analysis. Descriptive statistics were used for the baseline characteristics of the cohort, stratified by the presence or absence of one or more drug allergy labels. Continuous data are presented as mean (SD) or median (IQR) and categorical data as number (%). Hypothesis testing was not conducted on baseline data. The clinical care received, including the surgical procedure category and mode of anaesthesia, were summarised.

To investigate associations between the presence of drug allergy labels and complications, a mixed effects logistic regression (for binary outcome data) or mixed effects binomial regression (for count data) was performed with a random intercept for site, adjusted by all other recorded variables one at a time. Effect estimates were compared with the crude effect estimates for the main exposure (presence of drug allergy label). Covariates were included in the model based on clinical plausibility using a forced simultaneous entry approach. The baseline risk factors we considered were: age, gender, surgical procedure, current smoker, diabetes mellitus, ASA, wound contamination, duration of surgery, active cancer, liver

cirrhosis, obesity, and frailty. For the analysis of mortality, we included hypertension, heart failure, coronary artery disease, peripheral vascular disease, and asthma or COPD as covariates. All analyses were conducted using STATA version 17.0 or R 4.4.1. The results are reported with 95% confidence intervals (CI) and p-values. A significance level of $p < 0.05$ is considered statistically significant.

The inferential statistical analysis and modelling was conducted by Kamran Khan, statistician for the Critical care and Perioperative Medicine Research Group at Queen Mary University London, with funding provided through the National Institute of Academic Anaesthesia grant which I secured jointly with Dr Tom Abbott (WKRO-2020-0020).

2.4.4.3 Data validation and handling of missing data

The database was designed to minimise data entry errors by having validation measures in place. The electronic data collection form provided a warning message if data outside a pre-determined validity range were entered, with users prompted to check the value entered. Data were checked for duplicates, which were subsequently removed. A data validation process was conducted at all sites, who were asked to check source data for 3% of their patient cohort, selected at random by the central study team. Patients for whom primary outcome data were missing were excluded from the analysis. Prior to exclusion, substantial efforts were made to engage with the site and help them address this. For patients with <5% missing data, multiple imputation techniques were employed using R package mice 3.16.0.

2.5 Results

2.5.1 Descriptive statistics for the cohort

A total of 13,720 patient records were examined. Of these, 78 were excluded from further analysis (see Figure 13: Flow Diagram of Patients). Among included patients, there was 99% data completion for the variables used in the analyses below, and 100% of primary outcome data were complete.

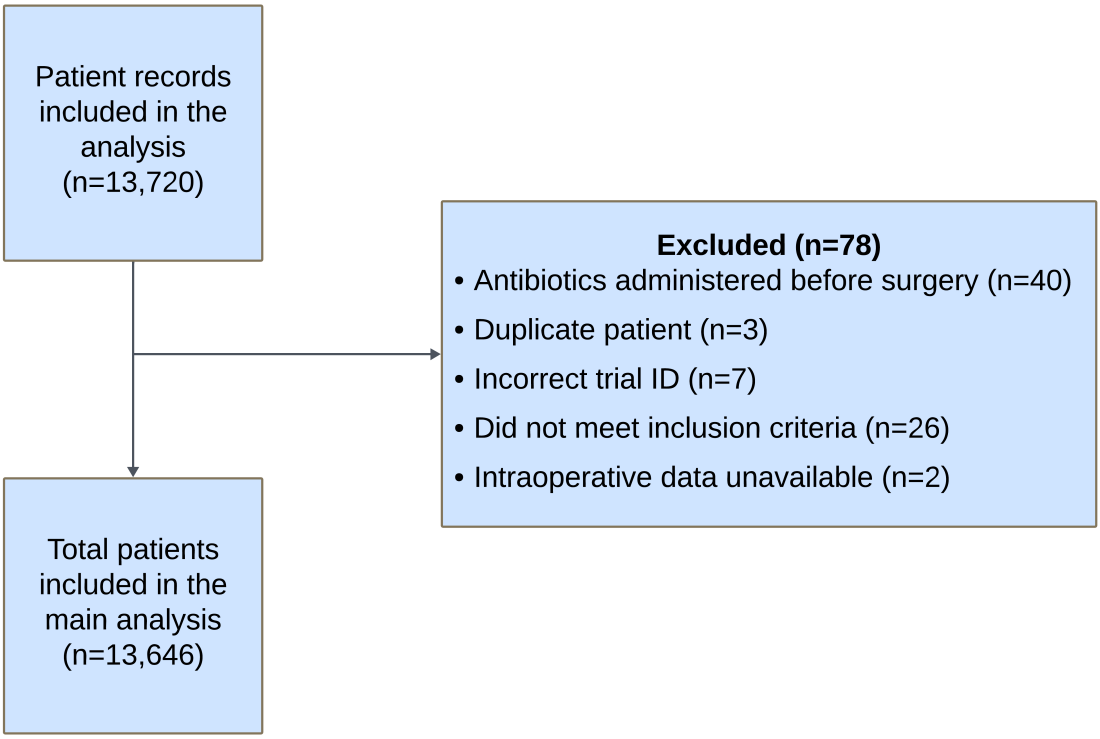


Figure 13: Flow diagram of patient inclusion and reasons for exclusion

Of a total of 13,646 patients in the study, 29% (3924/13,646) had one or more drug allergy labels recorded in their notes. See Table 5 for patient characteristics and clinical care, stratified by presence of absence of a drug allergy label, Table 6 for categories of drug allergy labels, and Table 7 for summary of complications within 30 days after surgery, stratified by presence or absence of drug allergy labels.

Table 5: Baseline and clinical care characteristics of included patients, stratified by presence or absence of drug allergy labels

Variable	**Number of participants with available data**	**Allergy Not reported** N = 9722(%)	**Allergy reported** N = 3924(%)
Sex	(100%)		
Female		6212 (64%)	2847 (73%)
Male		3510 (36%)	1077 (27%)
Age (years)	(100%)		
18-37		2401 (25%)	496 (13%)
38-57		2139 (22%)	794 (20%)
56-77		3512 (36%)	1622 (41%)
78 and above		1670 (17%)	1012 (26%)
Smoking Status	(100%)		
Not current smoker		8661 (89%)	3512 (90%)
Current smoker		1061 (11%)	412 (10%)
ASA Physical Status Classification	(100%)		
1		796 (8·2%)	143 (3·6%)
2		6144 (63%)	2085 (53%)
3		2623 (27%)	1544 (39%)
4		159 (1·6%)	152 (3·9%)
Obesity	(100%)		
0		7636 (79%)	3068 (78%)
1		2086 (21%)	856 (22%)
Liver Cirrhosis	(100%)		

Variable	Number of participants with available data	Allergy Not reported N = 9722(%)	Allergy reported N = 3924(%)
0		9680 (100%)	3896 (99%)
1		42 (0·4%)	28 (0·7%)
Heart Failure	(100%)	268 (2·8%)	219 (5·6%)
Hypertension	(100%)	3091 (32%)	1663 (42%)
Asthma/COPD	(100%)	1149 (12%)	851 (22%)
Diabetes Mellitus	(100%)		
0		8272 (85%)	3246 (83%)
1		1450 (15%)	678 (17%)
Active Cancer	(100%)		
0		7787 (80%)	3109 (79%)
1		1935 (20%)	815 (21%)
Coronary Artery Disease	(100%)	625 (6.4%)	397 (10%)
Stroke	(100%)	305 (3.1%)	181 (4.6%)
Anaesthetic Techniques	(100%)		
Epidural		131 (1·3%)	22 (0·6%)
General		5477 (56%)	2429 (62%)
None/not documented		38 (0·4%)	7 (0·2%)
Regional Nerve Block		106 (1·1%)	37 (0·9%)
Sedation		14 (0·1%)	7 (0·2%)
Spinal		3956 (41%)	1422 (36%)
General Anaesthesia type	(100%)		
Both Volatile & TIVA		87 (1·6%)	33 (1·4%)

Variable	**Number of participants with available data**	**Allergy Not reported** N = 9722(%)	**Allergy reported** N = 3924(%)
General (Not specified)		195 (3·6%)	94 (3·9%)
TIVA Only		1996 (36%)	916 (38%)
Volatile Only		3199 (58%)	1386 (57%)
General & Other anaesthetic used	(100%)		
General + Epidural		151 (2·8%)	64 (2·6%)
General + Spinal		1474 (27%)	635 (26%)
General alone		3852 (70%)	1730 (71%)
Open surgical technique used?	(100%)	6794 (70%)	2725 (69%)
Surgical Procedure category	(100%)		
Caesarean section		2260 (23%)	431 (11%)
Colorectal resection		1355 (14%)	588 (15%)
Hysterectomy		1504 (16%)	740 (19%)
Internal fixation of a closed long bone fractur		1426 (15%)	567 (14%)
Primary hip/knee replacement		1875 (19%)	1145 (29%)
Trans-urethral resection of prostate/bladder tumour		1281 (13%)	452 (12%)
Wound contamination during surgery	(100%)	82 (0·8%)	41 (1·0%)
Duration of surgery (Hrs.)	(99%)	2.28 (6·20)	2.49 (9·14)

Variable	**Number of participants with available data**	**Allergy Not reported** N = 9722(%)	**Allergy reported** N = 3924(%)
Duration of surgery (Hrs.)	(99%)		
0 - <2 hours		5593 (58%)	2005 (51%)
2 - <4 hours		2853 (30%)	1413 (36%)
4 - <6 hours		728 (7·6%)	311 (8·0%)
> 6 hours		461 (4·8%)	170 (4·4%)

Table 6: Category of drug allergy labels

Category of allergy	**Number of patients reporting the allergy (as % of overall cohort (13,646)** [1]
Penicillin	1573 (12%)
Analgesics (including NSAIDs and opioids)	1190 (9%)
Other, non-penicillin antimicrobial agents	874 (6%)
Adhesive tapes or plasters	87 (1%)
Induction agents and neuromuscular blocking agents	11 (<1%)
Drugs not commonly used during perioperative period*	1344 (10%)
Mis-recording of non-drug allergies**	83 (1%)

[1] *Total number of reported allergies (5171) is greater than number of patients reporting allergies (3924) due to reporting of multiple allergies*

*e.g. AdcalD3, ACEI, contrast media, intravenous iron preparations.

**e.g. aeroallergens, food allergens

Characteristic	**Allergy Not reported** N = 9,722[1]	**Allergy reported** N = 3,924[1]
Post-operative infections	1,472 (15%)	750 (19%)
Surgical site infection	760 (7.8%)	337 (8.6%)
Pneumonia	251 (2.6%)	192 (4.9%)
UTI – Non-TURP/TURBT	297 (3.1%)	179 (4.6%)
Bloodstream	57 (0.6%)	24 (0.6%)
Intracranial	1 (<0.1%)	1 (<0.1%)
Uncertain infection	278 (2.9%)	113 (2.9%)
Surgical site infections (SSI)	760 (7.8%)	337 (8.6%)
Superficial	396 (4.1%)	179 (4.6%)
Deep Surgical	137 (1.4%)	67 (1.7%)
Organ Space	118 (1.2%)	48 (1.2%)
UTI-TURP/TURBT	157 (1.6%)	70 (1.8%)
Post operative complications	1,926 (20%)	989 (25%)
Deaths	73 (0.8%)	48 (1.2%)
Post-operative infections	1,472 (15%)	750 (19%)
Allergic reaction	29 (0.3%)	31 (0.8%)
Acute kidney injury	528 (5.4%)	292 (7.4%)
Diarrhoea	46 (0.5%)	18 (0.5%)
Hearing loss	4 (<0.1%)	2 (<0.1%)
Tinnitus	1 (<0.1%)	1 (<0.1%)
Vertigo	4 (<0.1%)	4 (0.1%)
Anastomotic leak	41 (0.4%)	19 (0.5%)
ARDS	8 (<0.1%)	4 (0.1%)
Myocardial Infarction	11 (0.1%)	3 (<0.1%)

Postoperative bleed	97 (1.0%)	40 (1.0%)
Pulmonary embolism	24 (0.2%)	17 (0.4%)
Stroke	10 (0.1%)	12 (0.3%)
Side effects	564 (5.8%)	311 (7.9%)
Acute Kidney Injury	528 (5.4%)	292 (7.4%)
Diarrhoea	46 (0.5%)	18 (0.5%)
Hearing loss	4 (<0.1%)	2 (<0.1%)
Tinnitus	1 (<0.1%)	1 (<0.1%)
Vertigo	4 (<0.1%)	4 (0.1%)

[1]n (%)

Table 7: Summary of postoperative complications within 30 days after surgery, stratified by presence or absence of drug allergy labels

(Constituent events reported at the event level. A single patient experiencing multiple events is counted more than once. Composite outcomes are reported at the patient level).

2.5.2 Inferential analysis

2.5.2.1 Primary outcome

The presence of one or more drug allergy labels was associated with a 24% increase in the odds ratio of developing a surgical site infection within 30 days after surgery, compared with patients who did not report drug allergy (OR 1.24 (95%CI 1.09-1.40) p<0.001). See Table 8 for regression model, Table 15 for summary of odds ratios for primary and secondary outcomes, and Figure 14 for forest plot of odds ratios for primary and secondary outcomes.

Table 8: Mixed effects logistic regression examining the association between drug allergy labels and surgical site infections, adjusted for important clinical covariates

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.02 (0.02 to 0.04)	**<0.001**
Drug allergy		
Allergy Not reported	—	
Allergy reported	1.24 (1.09 to 1.40)	**<0.001**
Age		
18-37	—	
38-57	0.92 (0.74 to 1.15)	0.48
56-77	0.96 (0.75 to 1.23)	0.77
78 and above	1.04 (0.78 to 1.38)	0.80
Sex		
Female	—	
Male	1.08 (0.93 to 1.26)	0.32
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.21 (1.01 to 1.44)	**0.036**
Surgical procedure		
Primary hip/knee replacement	—	
Caesarean section	2.44 (1.78 to 3.32)	**<0.001**
Colorectal resection	2.59 (2.02 to 3.33)	**<0.001**
Hysterectomy	2.07 (1.62 to 2.63)	**<0.001**
Internal fixation of a closed long bone fracture	0.90 (0.70 to 1.15)	0.39
Trans-urethral resection of prostate/bladder tumour	2.77 (2.16 to 3.55)	**<0.001**
Wound contamination		
No	—	

Yes	2.57 (1.66 to 3.98)	**<0.001**
Surgery time (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.39 (1.17 to 1.66)	**<0.001**
4 - <6 hours	1.73 (1.35 to 2.22)	**<0.001**
> 6 hours	2.50 (1.88 to 3.31)	**<0.001**
Frailty		
No Frailty	—	
Mild Frailty	0.93 (0.78 to 1.12)	0.47
Moderate Frailty	1.04 (0.82 to 1.32)	0.74
Severe Frailty	1.83 (1.15 to 2.90)	**0.011**
ASA Physical Status Classification		
1	—	
2	1.22 (0.92 to 1.62)	0.17
3	1.75 (1.29 to 2.38)	**<0.001**
4	2.42 (1.53 to 3.83)	**<0.001**
Diabetes Mellitus	1.16 (1.00 to 1.35)	**0.046**
Heart Failure	0.96 (0.70 to 1.31)	0.80
Stroke	1.38 (1.05 to 1.80)	**0.019**
Hypertension	0.92 (0.80 to 1.05)	0.23
Coronary Artery Disease	0.89 (0.71 to 1.10)	0.29
Asthma/COPD	1.08 (0.92 to 1.26)	0.35
Peripheral Vascular Disease	0.76 (0.51 to 1.15)	0.20
Active Cancer	0.90 (0.77 to 1.04)	0.15
Liver Cirrhosis	0.93 (0.45 to 1.94)	0.85
Obesity	1.30 (1.13 to 1.49)	**<0.001**
centreid.sd__(Intercept)	0.60 (NA to NA)	

[1]Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.37, ICC = 0.10, N (centreid) = 23, Observations = 13,378, Marginal R^2/Conditional R^2 = 0.084/0.176

CI = Confidence Interval, OR = Odds Ratio

2.5.2.2 Secondary analyses

Postoperative infections were more common among patients with a drug allergy label compared to those without a label (750/3924 (19%) vs 1472/9722 (15%); OR 1·23 [1·10 – 1·78], p<0·001). See Table 9 for full regression model. Postoperative complications were more common among patients with a drug allergy label compared to those without a label (989/3924 (25%) vs 1926/9722 (20%); OR 1·19 [1·08 – 1·32] p<0·001). See Table 10 for full regression model. The presence of drug allergy label was associated with an increase in the total number of antimicrobial agents used until 30 days after surgery (mean (SD) 2·0 (1·1) vs 1·8 (1·0); OR 1·07 [1·05 - 1·11] p<0·001), and a three times greater risk of allergic reaction (31/3924 (0·8%) vs 29/9722 (0·3%); OR 3·00 [1·77 – 5·09] p<0·001). See Table 11 and 12, respectively. Drug allergy labels were not significantly associated with increased incidence of either antimicrobial side effects or postoperative mortality. See Tables 13 and 14, respectively.

Table 9: Mixed effects logistic regression examining association between drug allergy labels and postoperative infections

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.04 (0.02 to 0.05)	**<0.001**
Drug allergy		
Allergy Not reported	—	
Allergy reported	1.23 (1.10 to 1.37)	**<0.001**
Age		
18-37	—	
38-57	0.98 (0.80 to 1.19)	0.84

56-77	1.10 (0.89 to 1.37)	0.38
78 and above	1.40 (1.10 to 1.79)	**0.006**
Sex		
Female	—	
Male	1.14 (1.00 to 1.30)	**0.043**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.31 (1.13 to 1.53)	**<0.001**
Surgical procedure		
Primary hip/knee replacement	—	
Caesarean section	2.25 (1.73 to 2.94)	**<0.001**
Colorectal resection	2.29 (1.86 to 2.82)	**<0.001**
Hysterectomy	1.80 (1.47 to 2.20)	**<0.001**
Internal fixation of a closed long bone fracture	1.01 (0.83 to 1.21)	0.96
Trans-urethral resection of prostate/bladder tumour	1.52 (1.23 to 1.88)	**<0.001**
Wound contamination		
No	—	
Yes	2.13 (1.39 to 3.24)	**<0.001**
Surgery time (hrs)		
0 - <2 hours	—	
2 - <4 hours	1.39 (1.21 to 1.61)	**<0.001**

4 - <6 hours	1.76 (1.42 to 2.18)	**<0.001**
> 6 hours	2.64 (2.06 to 3.38)	**<0.001**
Frailty		
No Frailty	—	
Mild Frailty	1.13 (0.97 to 1.32)	0.11
Moderate Frailty	1.35 (1.12 to 1.64)	**0.002**
Severe Frailty	3.09 (2.15 to 4.44)	**<0.001**
ASA Physical Status Classification		
1	—	
2	1.25 (0.97 to 1.60)	0.084
3	1.74 (1.33 to 2.28)	**<0.001**
4	3.21 (2.20 to 4.68)	**<0.001**
Diabetes Mellitus	1.15 (1.02 to 1.31)	**0.029**
Heart Failure	1.03 (0.80 to 1.32)	0.82
Stroke	1.34 (1.04 to 1.73)	**0.024**
Hypertension	0.99 (0.88 to 1.11)	0.86
Coronary Artery Disease	0.99 (0.82 to 1.18)	0.87
Asthma/COPD	1.24 (1.09 to 1.42)	**0.001**
Peripheral Vascular Disease	1.03 (0.76 to 1.42)	0.83
Active Cancer	0.93 (0.82 to 1.06)	0.28
Liver Cirrhosis	0.60 (0.29 to 1.21)	0.15
Obesity	1.26 (1.12 to 1.42)	**<0.001**

centreid.sd__(Intercept)	0.63 (NA to NA)	

[1]*Random Effects: σ² (Residual) = 3.29, τ00 (centreid) = 0.39, ICC = 0.11, N (centreid) = 23, Observations = 13,378, Marginal R²/Conditional R² = 0.084/0.182*

Table 10: Mixed effects logistic regression examining association between drug allergy labels and postoperative complications

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.05 (0.03 to 0.07)	**<0.001**
Drug allergy		
Allergy Not reported	—	
Allergy reported	1.19 (1.08 to 1.32)	**<0.001**
Age		
18-37	—	
38-57	1.13 (0.94 to 1.35)	0.21
56-77	1.26 (1.03 to 1.54)	**0.025**
78 and above	1.83 (1.46 to 2.30)	**<0.001**
Sex		
Female	—	
Male	1.17 (1.04 to 1.32)	**0.008**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.19 (1.03 to 1.37)	**0.018**
Surgical procedure		
Primary hip/knee replacement	—	
Caesarean section	1.98 (1.56 to 2.51)	**<0.001**
Colorectal resection	1.80 (1.49 to 2.17)	**<0.001**

Hysterectomy	1.36 (1.13 to 1.63)	**<0.001**
Internal fixation of a closed long bone fracture	1.04 (0.88 to 1.22)	0.66
Trans-urethral resection of prostate/bladder tumour	1.15 (0.96 to 1.39)	0.14
Wound contamination		
No	—	
Yes	2.40 (1.61 to 3.58)	**<0.001**
Surgery time (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.41 (1.24 to 1.60)	**<0.001**
4 - <6 hours	1.76 (1.44 to 2.14)	**<0.001**
> 6 hours	3.16 (2.51 to 3.99)	**<0.001**
Frailty		
No Frailty	—	
Mild Frailty	1.14 (0.99 to 1.31)	0.060
Moderate Frailty	1.45 (1.22 to 1.72)	**<0.001**
Severe Frailty	3.58 (2.52 to 5.10)	**<0.001**
ASA Physical Status Classification		
1	—	
2	1.32 (1.05 to 1.65)	**0.019**
3	1.88 (1.47 to 2.41)	**<0.001**
4	3.18 (2.24 to 4.53)	**<0.001**
Diabetes Mellitus	1.24 (1.10 to 1.39)	**<0.001**
Heart Failure	1.25 (1.00 to 1.55)	**0.048**
Stroke	8.65 (2.20 to 34.0)	**0.002**
Hypertension	1.06 (0.96 to 1.18)	0.27
Coronary Artery Disease	1.06 (0.91 to 1.25)	0.45
Asthma/COPD	1.20 (1.06 to 1.35)	**0.003**
Peripheral Vascular Disease	0.98 (0.74 to 1.31)	0.91

Active Cancer	1.00 (0.89 to 1.13)	0.97
Liver Cirrhosis	0.98 (0.56 to 1.73)	0.96
Obesity	1.19 (1.06 to 1.33)	**0.002**
centreid.sd__(Intercept)	0.50 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, $\tau 00$ (centreid) = 0.25, ICC = 0.07, N (centreid) = 23, Observations = 13,378, Marginal R^2/Conditional R^2 = 0.127/0.189*

Table 11: Mixed effects negative binomial regression examining association between drug allergy labels and total number of antimicrobial agents administered

Characteristic[1]	**exp(Beta) (95% CI)**	**p-value**
(Intercept)	1.71 (1.58 to 1.85)	**<0.001**
Patient reported allergies		
Allergy reported	1.07 (1.05 to 1.11)	**<0.001**
Age		
18-37	—	
38-57	0.97 (0.92 to 1.02)	0.22
56-77	1.00 (0.95 to 1.05)	0.98
78 and above	1.06 (1.00 to 1.13)	0.055
Sex		
Female	—	
Male	1.04 (1.00 to 1.07)	**0.026**
Smoking Status		

Current Smoker(N)	—	
Current Smoker(Y)	1.04 (1.00 to 1.08)	0.058
Surgical Procedure category		
Caesarean section	—	
Colorectal resection	1.19 (1.11 to 1.28)	**<0.001**
Hysterectomy	0.89 (0.83 to 0.95)	**<0.001**
Internal fixation of a closed long bone fracture	0.88 (0.83 to 0.94)	**<0.001**
Primary hip/knee replacement	0.79 (0.74 to 0.84)	**<0.001**
Trans-urethral resection of prostate/bladder tumour	0.70 (0.65 to 0.75)	**<0.001**
Wound contamination during surgery		
No	—	
Yes	1.10 (0.98 to 1.23)	0.095
Duration of surgery (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.07 (1.03 to 1.11)	**<0.001**
4 - <6 hours	1.13 (1.07 to 1.19)	**<0.001**
> 6 hours	1.35 (1.26 to 1.44)	**<0.001**
Frailty		
No Frailty	—	
Mild Frailty	1.01 (0.97 to 1.05)	0.76
Moderate Frailty	1.05 (1.00 to 1.11)	**0.043**

Severe Frailty	1.22 (1.09 to 1.36)	**<0.001**
ASA Physical Status Classification		
1	—	
2	1.07 (1.01 to 1.13)	**0.017**
3	1.14 (1.07 to 1.21)	**<0.001**
4	1.31 (1.19 to 1.45)	**<0.001**
Diabetes Mellitus		
0	—	
1	1.03 (0.99 to 1.07)	0.11
Heart Failure	1.00 (0.93 to 1.07)	0.90
Stroke	1.10 (1.03 to 1.18)	**0.006**
Hypertension	0.98 (0.95 to 1.01)	0.27
Coronary Artery Disease	1.00 (0.95 to 1.05)	0.91
Asthma/COPD	1.05 (1.02 to 1.09)	**0.004**
Peripheral Vascular Disease	1.00 (0.91 to 1.09)	0.93
Active Cancer		
0	—	
1	0.98 (0.95 to 1.02)	0.30
Liver Cirrhosis		
0	—	
1	0.95 (0.80 to 1.12)	0.53
Obesity		

0	—	
1	1.03 (1.00 to 1.06)	0.089
centreid.sd__(Intercept)	0.12 (1,452,313 to 652,376,913)	

[1]*Random Effects: σ² (Residual) = 0.43, τ00 (centreid) = 0.02, ICC = 0.03, N (centreid) = 23, Observations = 13,378, Marginal R² = 0.086/ Conditional R² = 0.117*

Table 12: Mixed effects logistic regression examining association between drug allergy labels and allergic reactions

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.00 (0.00 to 0.00)	**<0.001**
Drug allergy		
Allergy Not reported	—	
Allergy reported	3.00 (1.77 to 5.09)	**<0.001**
Sex		
Female	—	
Male	1.07 (0.60 to 1.91)	0.81
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	0.87 (0.37 to 2.05)	0.75
Frailty		
No Frailty	—	
Mild Frailty	0.63 (0.24 to 1.65)	0.35
Moderate Frailty	1.91 (0.83 to 4.41)	0.13

Severe Frailty	1.63 (0.21 to 12.6)	0.64
Diabetes Mellitus	0.64 (0.30 to 1.38)	0.26
Heart Failure	1.02 (0.29 to 3.60)	0.97
Hypertension	0.81 (0.45 to 1.45)	0.47
Coronary Artery Disease	1.92 (0.82 to 4.46)	0.13
Asthma/COPD	0.82 (0.40 to 1.72)	0.61
Peripheral Vascular Disease	0.67 (0.09 to 4.93)	0.69
Active Cancer	2.11 (1.21 to 3.67)	**0.008**
Obesity	1.12 (0.61 to 2.06)	0.70
centreid.sd__(Intercept)	1.06 (NA to NA)	

[1]Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 1.13, ICC = 0.26, N (centreid) = 23, Observations = 13,646, Marginal R^2/Conditional R^2 = 0.094/0.326

Table 13: Mixed effects logistic regression examining association between drug allergy labels and antimicrobial side effects

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.02 (0.01 to 0.03)	**<0.001**
Drug allergy		
Allergy Not reported	—	
Allergy reported	1.11 (0.96 to 1.28)	0.16
Age		
18-37	—	
38-57	1.41 (1.02 to 1.96)	**0.040**
56-77	1.61 (1.14 to 2.28)	**0.006**
78 and above	2.45 (1.70 to 3.54)	**<0.001**

Sex		
Female	—	
Male	1.27 (1.08 to 1.48)	**0.003**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	0.99 (0.79 to 1.23)	0.90
Surgical procedure		
Primary hip/knee replacement	—	
Caesarean section	1.06 (0.71 to 1.58)	0.77
Colorectal resection	1.21 (0.93 to 1.56)	0.16
Hysterectomy	0.72 (0.55 to 0.95)	**0.018**
Internal fixation of a closed long bone fracture	1.04 (0.84 to 1.29)	0.72
Trans-urethral resection of prostate/bladder tumour	0.69 (0.53 to 0.90)	**0.006**
Wound contamination		
No	—	
Yes	1.91 (1.17 to 3.14)	**0.010**
Surgery time		
0 - <2 hours	—	
2 - <4 hours	1.47 (1.23 to 1.75)	**<0.001**
4 - <6 hours	1.76 (1.32 to 2.34)	**<0.001**
> 6 hours	3.64 (2.68 to 4.95)	**<0.001**
Frailty		
No Frailty	—	
Mild Frailty	1.35 (1.12 to 1.63)	**0.002**
Moderate Frailty	1.66 (1.33 to 2.07)	**<0.001**
Severe Frailty	2.75 (1.83 to 4.12)	**<0.001**

ASA Physical Status Classification		
1	—	
2	1.33 (0.90 to 1.97)	0.15
3	1.79 (1.19 to 2.69)	**0.005**
4	2.40 (1.45 to 3.98)	**<0.001**
Diabetes Mellitus	1.39 (1.19 to 1.64)	**<0.001**
Heart Failure	1.33 (1.03 to 1.73)	**0.031**
Stroke	10.7 (3.43 to 33.0)	**<0.001**
Hypertension	1.17 (1.01 to 1.35)	**0.039**
Coronary Artery Disease	1.19 (0.97 to 1.47)	0.090
Asthma/COPD	1.02 (0.86 to 1.21)	0.84
Peripheral Vascular Disease	0.86 (0.59 to 1.26)	0.44
Active Cancer	1.08 (0.91 to 1.29)	0.36
Liver Cirrhosis	1.11 (0.54 to 2.29)	0.77
Obesity	0.92 (0.78 to 1.10)	0.37
centreid.sd__(Intercept)	0.38 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.14, ICC = 0.04, N (centreid) = 23, Observations = 13,378, Marginal R^2/Conditional R^2 = 0.185/0.220*

Table 14: Mixed effects logistic regression examining association between drug allergy labels and mortality

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.00 (0.00 to 0.00)	**<0.001**
Drug allergy		
Allergy Not reported	—	

Allergy reported	1.19 (0.75 to 1.88)	0.47
Sex		
Female	—	
Male	2.28 (1.43 to 3.62)	**<0.001**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	0.63 (0.27 to 1.47)	0.29
Wound contamination		
No	—	
Yes	1.49 (0.20 to 11.1)	0.70
Frailty		
No Frailty	—	
Mild Frailty	2.97 (1.46 to 6.03)	**0.003**
Moderate Frailty	13.0 (7.18 to 23.5)	**<0.001**
Severe Frailty	43.9 (21.2 to 91.2)	**<0.001**
Diabetes Mellitus	0.93 (0.54 to 1.60)	0.78
Heart Failure	0.72 (0.34 to 1.52)	0.39
Stroke	2.44 (1.75 to 3.40)	**<0.001**
Hypertension	0.98 (0.62 to 1.55)	0.93
Coronary Artery Disease	1.39 (0.80 to 2.42)	0.24
Asthma/COPD	1.31 (0.79 to 2.20)	0.30
Peripheral Vascular Disease	1.67 (0.73 to 3.83)	0.22

Active Cancer	1.58 (0.98 to 2.54)	0.063
Liver Cirrhosis	1.02 (0.13 to 8.06)	0.99
Obesity	1.04 (0.57 to 1.90)	0.90
centreid.sd__(Intercept)	0.32 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, $\tau 00$ (centreid) = 0.10, ICC = 0.03, N (centreid) = 23, Observations = 13,468, Marginal R^2/Conditional R^2 = 0.248/0.271*

Table 15: Summary of primary and secondary outcomes

Outcomes	Drug allergy reported[a]	Drug allergy *not* reported[b]	Effect size in patients with reported drug allergy Odds ratio (95% CI)	P-value
Primary outcome				
Surgical site infection	337 (8·6%)	760 (7·8%)	1·24 (1·09 – 1.40)	**<0·001[1]**
Secondary outcomes				
Postoperative infections n (%)	750 (19%)	1472 (15%)	1·23 (1·10 – 1·37)	**<0·001[2]**
Postoperative complications[c] n (%)	989 (25%)	1926 (20%)	1·19 (1·08 – 1·32)	**<0·001[3]**
Number of antimicrobial agents administered mean (SD)	2·0 (1·1)	1·8 (1·0)	1·07 (1·05 - 1·11)	**<0·001[4]**
Antimicrobial side effects[e] n (%)	311 (7·9%)	564 (5·8%)	1·11 (0·96 – 1·28)	0·16
Allergic reactions n (%)	31 (0·8%)	29 (0·3%)	3·00 (1·77 – 5·09)	**<0·001**
Death n (%)	36 (0.9%)	54 (0·6%)	1·19 (0·75 – 1·88)	0·47

1-4 See tables above for full regression models

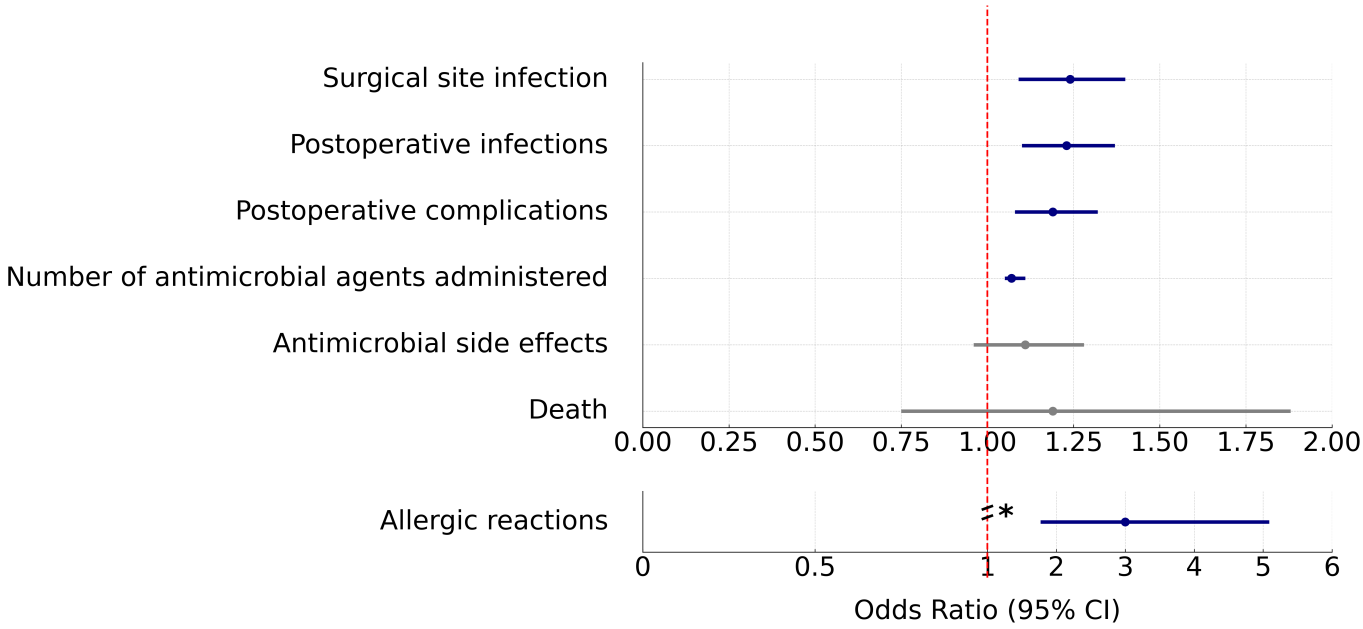
a,b Data available for 100% of patients

c Surgical site infection, pneumonia, urinary tract infection, abscess or collection, bloodstream infection, intracranial infection, meningitis, infection of uncertain source.

d Composite outcome of postoperative infection, anastomotic leak, ARDS, myocardial infarction, postoperative bleed, pulmonary embolism, stroke, diarrhoeal illness, hearing loss, vertigo, tinnitus, acute kidney injury, allergic reaction, death

e Diarrhoeal illness, vertigo, tinnitus, acute kidney injury, allergic reaction to antimicrobial agent

Figure 14: Forest plot displaying odds ratios for primary and secondary outcomes



*Indicates a compressed scale for presentation of the odds ratio for incidence of allergic reactions.

Significant findings are highlighted in blue. The x axis shows odds ratios and the error bars show 95% confidence intervals.

2.5.2.3 Sensitivity analyses

Patients with a penicillin allergy label experienced a substantially increased risk of surgical site infection compared to those without any label of drug allergy (penicillin allergy label 209/1573 (13%) vs no label 1002/9722 (10%); OR 1·35 [1·14 – 1·60] p<0·001). See Table 16.

Postoperative complications were also increased among those with a penicillin allergy label (penicillin allergy label 388/1573 (25%) vs no allergy label 1901/9722 (20%); OR 1·23 [1·07 – 1·41] p<0·003), and a greater number of different antimicrobial agents were used from recruitment to 30 days following surgery, in those labelled penicillin allergic (mean (IQR) among those with penicillin allergy 2·00 (1·00-3·00) vs no allergy label 2·00 (1·00-2·00); OR 1·16 [1·11 – 1·20] p<0·001). See Tables 17 and 18 respectively. There was no difference in the incidence of antimicrobial side effects between patients with or without a penicillin allergy label. See Table 19. For patients with non-penicillin drug allergy labels, significantly increased risk of surgical site infection, postoperative complications, and number of antimicrobials used were observed, although with effect sizes were smaller than those for patients with penicillin allergy labels.

Table 16: Mixed effects logistic regression examining association between drug allergy categories and surgical site infection

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.02 (0.01 to 0.03)	**<0.001**
Allergy Categories		
No allergy	—	
Non-penicillin	1.16 (1.00 to 1.35)	**0.047**
Penicillin	1.35 (1.14 to 1.60)	**<0.001**
Age		
18-37	—	
38-57	0.92 (0.74 to 1.15)	0.45
56-77	0.96 (0.75 to 1.22)	0.73
78 and above	1.04 (0.78 to 1.37)	0.80
Sex		
Female	—	

Male	1.08 (0.93 to 1.26)	0.32
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.20 (1.00 to 1.43)	**0.044**
Surgical Procedure category		
Primary hip/knee replacement	—	
Caesarean section	2.39 (1.75 to 3.25)	**<0.001**
Colorectal resection	2.59 (2.02 to 3.33)	**<0.001**
Hysterectomy	2.07 (1.63 to 2.63)	**<0.001**
Internal fixation of a closed long bone fracture	0.90 (0.70 to 1.15)	0.40
Trans-urethral resection of prostate/bladder tumour	2.76 (2.15 to 3.53)	**<0.001**
Wound contamination		
No	—	
Yes	2.56 (1.65 to 3.96)	**<0.001**
Duration of surgery (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.39 (1.17 to 1.66)	**<0.001**
4 - <6 hours	1.72 (1.34 to 2.21)	**<0.001**
> 6 hours	2.49 (1.88 to 3.30)	**<0.001**
Frailty		
Non-frail	—	
Mild Frailty	0.94 (0.78 to 1.12)	0.48
Moderate Frailty	1.05 (0.83 to 1.32)	0.71
Severe Frailty	1.84 (1.16 to 2.92)	**0.009**
ASA Physical Status Classification	1.39 (1.24 to 1.56)	**<0.001**
Diabetes Mellitus	1.17 (1.00 to 1.35)	**0.044**

Heart Failure	0.96 (0.71 to 1.32)	0.82
Stroke	1.38 (1.05 to 1.80)	**0.019**
Hypertension	0.92 (0.80 to 1.05)	0.23
Coronary Artery Disease	0.90 (0.72 to 1.12)	0.34
Asthma/COPD	1.08 (0.92 to 1.26)	0.36
Peripheral Vascular Disease	0.77 (0.51 to 1.16)	0.20
Active Cancer	0.90 (0.77 to 1.04)	0.15
Liver Cirrhosis	0.94 (0.45 to 1.96)	0.88
Obesity	1.30 (1.13 to 1.49)	**<0.001**
centreid.sd__(Intercept)	0.60 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.37 ICC = 0.10, N (centreid) = 23, Observations = 13,378, Marginal R^2 = 0.085/ Conditional R^2 = 0.176*

Table 17: Mixed effects logistic regression examining association between drug allergy label categories and postoperative complications

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.03 (0.02 to 0.04)	**<0.001**
Allergy Categories		
No allergy	—	
Non-penicillin	1.18 (1.05 to 1.33)	**0.005**
Penicillin	1.23 (1.07 to 1.41)	**0.003**
Age		
18-37	—	
38-57	1.11 (0.93 to 1.34)	0.25
56-77	1.23 (1.01 to 1.50)	**0.044**

78 and above	1.77 (1.41 to 2.21)	**<0.001**
Sex		
Female	—	
Male	1.17 (1.04 to 1.32)	**0.008**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.18 (1.03 to 1.37)	**0.019**
Surgical Procedure category		
Primary hip/knee replacement	—	
Caesarean section	1.95 (1.54 to 2.48)	**<0.001**
Colorectal resection	1.82 (1.50 to 2.20)	**<0.001**
Hysterectomy	1.37 (1.14 to 1.64)	**<0.001**
Internal fixation of a closed long bone fracture	1.02 (0.86 to 1.20)	0.83
Trans-urethral resection of prostate/bladder tumour	1.16 (0.96 to 1.40)	0.12
Wound contamination		
No	—	
Yes	2.35 (1.58 to 3.50)	**<0.001**
Duration of surgery (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.41 (1.24 to 1.60)	**<0.001**
4 - <6 hours	1.75 (1.43 to 2.14)	**<0.001**
> 6 hours	3.14 (2.49 to 3.97)	**<0.001**
Frailty		
Non-frail	—	
Mild Frailty	1.14 (0.99 to 1.30)	0.072

Moderate Frailty	1.43 (1.20 to 1.69)	**<0.001**
Severe Frailty	3.47 (2.45 to 4.93)	**<0.001**
ASA Physical Status Classification	1.45 (1.33 to 1.59)	**<0.001**
Diabetes Mellitus	1.24 (1.10 to 1.39)	**<0.001**
Heart Failure	1.21 (0.97 to 1.50)	0.090
Stroke	8.82 (2.22 to 35.1)	**0.002**
Hypertension	1.07 (0.96 to 1.18)	0.23
Coronary Artery Disease	1.02 (0.87 to 1.20)	0.78
Asthma/COPD	1.19 (1.05 to 1.34)	**0.006**
Peripheral Vascular Disease	0.98 (0.74 to 1.31)	0.90
Active Cancer	0.99 (0.87 to 1.11)	0.82
Liver Cirrhosis	0.93 (0.53 to 1.65)	0.81
Obesity	1.17 (1.05 to 1.31)	**0.005**
centreid.sd__(Intercept)	0.51 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.26 ICC = 0.07, N (centreid) = 23, Observations = 13,378, Marginal R^2 = 0.127/ Conditional R^2 = 0.189*

Table 18: Mixed effects negative binomial regression examining association between drug allergy categories and total number of antimicrobial agents used

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.03 (0.02 to 0.04)	**<0.001**
Allergy Categories		
No allergy	—	

Non-penicillin	1.18 (1.05 to 1.33)	**0.005**
Penicillin	1.23 (1.07 to 1.41)	**0.003**
Age		
18-37	—	
38-57	1.11 (0.93 to 1.34)	0.25
56-77	1.23 (1.01 to 1.50)	**0.044**
78 and above	1.77 (1.41 to 2.21)	**<0.001**
Sex		
Female	—	
Male	1.17 (1.04 to 1.32)	**0.008**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	1.18 (1.03 to 1.37)	**0.019**
Surgical Procedure category		
Primary hip/knee replacement	—	
Caesarean section	1.95 (1.54 to 2.48)	**<0.001**
Colorectal resection	1.82 (1.50 to 2.20)	**<0.001**
Hysterectomy	1.37 (1.14 to 1.64)	**<0.001**
Internal fixation of a closed long bone fracture	1.02 (0.86 to 1.20)	0.83
Trans-urethral resection of prostate/bladder tumour	1.16 (0.96 to 1.40)	0.12
Wound contamination		
No	—	
Yes	2.35 (1.58 to 3.50)	**<0.001**
Duration of surgery (Hrs)		
0 - <2 hours	—	

2 - <4 hours	1.41 (1.24 to 1.60)	**<0.001**
4 - <6 hours	1.75 (1.43 to 2.14)	**<0.001**
> 6 hours	3.14 (2.49 to 3.97)	**<0.001**
Frailty		
Non-frail	—	
Mild Frailty	1.14 (0.99 to 1.30)	0.072
Moderate Frailty	1.43 (1.20 to 1.69)	**<0.001**
Severe Frailty	3.47 (2.45 to 4.93)	**<0.001**
ASA Physical Status Classification	1.45 (1.33 to 1.59)	**<0.001**
Diabetes Mellitus	1.24 (1.10 to 1.39)	**<0.001**
Heart Failure	1.21 (0.97 to 1.50)	0.090
Stroke	8.82 (2.22 to 35.1)	**0.002**
Hypertension	1.07 (0.96 to 1.18)	0.23
Coronary Artery Disease	1.02 (0.87 to 1.20)	0.78
Asthma/COPD	1.19 (1.05 to 1.34)	**0.006**
Peripheral Vascular Disease	0.98 (0.74 to 1.31)	0.90
Active Cancer	0.99 (0.87 to 1.11)	0.82
Liver Cirrhosis	0.93 (0.53 to 1.65)	0.81
Obesity	1.17 (1.05 to 1.31)	**0.005**
centreid.sd__(Intercept)	0.51 (NA to NA)	

[1]Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.26 ICC = 0.07, N (centreid) = 23, Observations = 13,378, Marginal R^2 = 0.127/ Conditional R^2 = 0.189

Table 19: Mixed effects logistic regression examining association between drug allergy categories and antimicrobial side effects

Characteristic[1]	**OR (95% CI)**	**p-value**
(Intercept)	0.01 (0.01 to 0.02)	**<0.001**
Allergy Categories		
No allergy	—	
Non-penicillin	1.15 (0.98 to 1.36)	0.090
Penicillin	1.02 (0.83 to 1.26)	0.82
Age		
18-37	—	
38-57	1.41 (1.02 to 1.96)	**0.039**
56-77	1.61 (1.14 to 2.27)	**0.006**
78 and above	2.43 (1.69 to 3.50)	**<0.001**
Sex		
Female	—	
Male	1.27 (1.09 to 1.49)	**0.003**
Current Smoker		
Current Smoker(N)	—	
Current Smoker(Y)	0.98 (0.79 to 1.22)	0.87
Surgical Procedure category		
Primary hip/knee replacement	—	
Caesarean section	1.07 (0.72 to 1.59)	0.75
Colorectal resection	1.22 (0.94 to 1.58)	0.14
Hysterectomy	0.73 (0.55 to 0.96)	**0.023**
Internal fixation of a closed long bone fracture	1.05 (0.84 to 1.30)	0.67
Trans-urethral resection of prostate/bladder tumour	0.70 (0.53 to 0.91)	**0.008**

Wound contamination		
No	—	
Yes	1.92 (1.17 to 3.15)	**0.010**
Duration of surgery (Hrs)		
0 - <2 hours	—	
2 - <4 hours	1.46 (1.22 to 1.74)	**<0.001**
4 - <6 hours	1.75 (1.31 to 2.32)	**<0.001**
> 6 hours	3.62 (2.66 to 4.91)	**<0.001**
Frailty		
Non-frail	—	
Mild Frailty	1.35 (1.12 to 1.63)	**0.002**
Moderate Frailty	1.66 (1.33 to 2.08)	**<0.001**
Severe Frailty	2.76 (1.84 to 4.13)	**<0.001**
ASA Physical Status Classification	1.34 (1.18 to 1.53)	**<0.001**
Diabetes Mellitus	1.39 (1.19 to 1.64)	**<0.001**
Heart Failure	1.34 (1.03 to 1.74)	**0.028**
Stroke	10.6 (3.44 to 32.8)	**<0.001**
Hypertension	1.18 (1.02 to 1.36)	**0.030**
Coronary Artery Disease	1.18 (0.96 to 1.45)	0.12
Asthma/COPD	1.02 (0.86 to 1.22)	0.81
Peripheral Vascular Disease	0.86 (0.59 to 1.27)	0.46
Active Cancer	1.08 (0.91 to 1.28)	0.37
Liver Cirrhosis	1.10 (0.53 to 2.27)	0.80
Obesity	0.93 (0.78 to 1.10)	0.38
centreid.sd__(Intercept)	0.38 (NA to NA)	

[1]*Random Effects: σ^2 (Residual) = 3.29, τ_{00} (centreid) = 0.15 ICC = 0.04, N (centreid) = 23, Observations = 13,378, Marginal R^2 = 0.185/ Conditional R^2 = 0.220*

2.6 Discussion

The principal finding of this study is that drug allergy labels, present in 29% of the cohort, were associated with a 24% increase in the incidence of surgical site infections after adjusting for clinically relevant confounders. In addition, the presence of a label was significantly associated with the risk of infective complications, postoperative complications, administration of an increased total number of antimicrobial agents from recruitment to 30 days after surgery, and incidence of allergic reactions within 30 days after surgery. With more than 5 million patients undergoing surgery every year in the UK, and an estimated 330 million surgical procedures performed globally each year, this represents a very substantial burden of preventable harm and increased healthcare costs (162-164).

The baseline characteristics of this cohort confirm previous data demonstrating a high prevalence of drug allergy labelling in surgical patients. There is an estimated global prevalence of drug allergy of up to 36%, with surgical patients more likely to report this than many other patient groups (52-54, 93, 94). A UK study I led in 2018 (DALES) found 29% of 21,219 elective surgical patients reported at least one drug allergy label, most commonly to antibiotics or analgesics (1). The consistency around prevalence of drug allergy labels between DALES and SAPPHIRE, increases confidence in the reliability and generalisability of the data presented in this thesis. The data on high prevalence of penicillin allergy labels is also consistent with estimated UK and global prevalence (96, 97, 165-167).

The causal mechanism(s) underpinning the effects seen in this study remain unclear, but may be driven in part by the presence of a penicillin allergy label. This allergy was reported by 12% of the overall cohort and accounted for 43% of all reported drug allergies. The presence of this label was associated with a 35% increase in the risk of surgical site infections and 23% increase in the composite outcome of all postoperative complications. Patients with this label received a greater number of antimicrobial agents during and after surgery and were at greater risk of requiring >10 doses of antimicrobial therapy (data not presented here), compared to those without the label. The potential harms associated with the label of penicillin allergy have been described previously in this thesis and elsewhere, and include increased risk of infection, increased infection with multi-resistant organisms, longer hospital

stays, increased rates of treatment failure and readmission, and higher all-cause mortality (2, 4, 95-98, 100, 108, 110, 153). Among surgical patients, a penicillin allergy label has previously been associated with an increased risk of surgical site infections, with a systematic review and meta-analysis conducted in 2025 demonstrating a 60% increase in the odds ratio for this outcome (OR 1.60 95%CI 1.27-2.01 $p<0.0001$) (3, 102, 154). However, these data must be interpreted cautiously since many of the studies included in the meta-analysis were single centre and retrospective, and did not adjust for important covariates known to be associated with negative health outcomes. The SAPPHIRE data provide the first robust, generalisable UK data on risk of surgical site infection in patients with a penicillin allergy label, adjusted for important covariates. Furthermore, SAPPHIRE provides novel data on the association between penicillin allergy and other postoperative complications – with associations seen for both infective and non-infective complications. Whilst not determining the causal nature of these associations, the data do provide clear evidence of an association with increased harm.

This study also demonstrates that non-penicillin allergy labels are associated with poor outcomes. This aligns with a very limited pool of evidence in the literature suggesting increased risk of post operative complications among patients with (non-penicillin) drug allergy labels. In particular, the presence of analgesic allergy labels has been linked to increased harm, although the strength and nature of this association is unknown (86, 87). In SAPPHIRE, the second largest category of drug allergy labels were common analgaesic medications including opioids and NSAIDs. It is biologically plausible that these patients may experience greater pain in the postoperative period, leading to reduced cough strength and poor mobility, in turn resulting in increased risk of chest infections and thrombo-embolic events. Avoidance of other drugs used during surgery, such as medical dyes or iodinated skin preparation, might also lead to less effective, or delayed, surgical care.

Whilst these data provide a strong signal that drug allergy labels are associated with harm, further research is required to elucidate the precise, underlying mechanisms for the effects seen in this study and determine whether removal of the drug allergy label mitigates or removes this association. As outlined in Chapter 2, a high proportion of drug allergy labels are incorrect when tested. Labels can be applied when the patient experiences recognised side

effects of a drug, such as nausea and vomiting with antibiotics, pruritis with opioids, or palpitations following the use of local anaesthetic with adrenaline. Sometimes symptoms caused by concurrent infection are misattributed to an allergic reaction, for example viral rashes in children which are misattributed to antibiotic allergy. At other times, idiosyncratic reactions or common physiological responses are attributed to allergy, for example vaso-vagal responses to dental procedures performed using local anaesthetic. Many patients avoid drugs purely based on a family history of allergy, without any personal experience of taking the drug or having a reaction to it. The allergy label can be applied by the patient themselves or by healthcare professionals, almost invariably without any confirmatory testing by an allergy specialist. Once the label is in place, limited access to specialist testing as well as logistical barriers to amending health records, makes it very difficult to remove (89-91, 168). This is also the case in the surgical population, for whom timely access to drug allergy testing is essentially inaccessible in the NHS. The harms associated with drug avoidance are not always obvious to surgical prescribers, including anaesthetists, for whom the overriding concern is of avoiding the immediate risk of a perioperative allergic reaction (92). Longer term harms, such as increased risk of treatment failure from avoidance of first-line antimicrobial options, are 'downstream' of the surgical episode and only visible with population-level research.

This study has several strengths. The selected surgical procedures, large number of sites, high data completion rates, and well-balanced recruitment across the selected surgical procedures, means that the results are likely to be generalisable to surgical patients in high income countries. The use of multivariable regression analysis to adjust the analyses for the presence of known confounding variables further strengthens the findings. However, as for all observational studies there are likely to be unmeasured confounders which may have introduced bias. Other important limitations include the lack of primary care data, which meant that complications occurring post-discharge and managed in the community were not captured. The most likely effect of this an under-estimation of the incidence of postoperative complications and therefore the degree of association between variables. The international generalisability of this data may be limited by the varying patterns of antimicrobial usage in

other countries. Lastly, whilst the findings provide a strong signal of harm associated with drug allergy labels, this does not provide evidence of causal effect.

2.7 Key messages

The presence of drug allergy labels is associated with a substantial increase in the risk of postoperative complications among surgical patients. This effect appears to be mediated in part by increased infections seen among patients with a penicillin allergy label, although patients with other drug allergy labels also experienced increased harm. The precise mechanisms underpinning these association remain unknown. Further research is needed to elucidate these mechanisms and to determine whether the pre-operative removal of drug allergy labels mitigates these harms.

3 Spurious Penicillin Allergy in Secondary Care: SPACE study

3.1 Background

Penicillin allergy is the most prevalent drug allergy reported in the UK and globally, with an estimated 6-20% carrying this label (4, 54, 157) . The label occurs more frequently with age and with increasing co-morbidity, and the in-patient population is more likely to carry the label than the general population. The harms associated with penicillin avoidance are detailed in Chapters 1 and 2 but, in brief, include an increased overall risk of infection, increased infection with methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile* and vancomycin-resistant enterococcus, longer hospital stays, more frequent admissions to critical care, and increased mortality (2, 4, 97, 99, 101). A 50% increase in the absolute risk of surgical site infections (SSIs) has been demonstrated in surgical patients (3). To date, few studies have demonstrated improved health outcomes following removal of the label. The ALABAMA study, completed in 2024, demonstrated increased use of penicillin antibiotics and reduced overall use of antibiotics in the 12 months following delabelling, but the long-term health outcomes for these patients remain known (169). The weight of epidemiological evidence nevertheless provides a strong signal that penicillin allergy delabelling is likely to benefit individuals and contribute to the wider ambition of improved antimicrobial stewardship at population level.

The current standard of care for patients with an unsubstantiated penicillin allergy label involves referral to an allergy specialist (primary qualification in allergy and/or immunology), with review of hospital and primary care records where possible, to assess the risk of genuine allergy (59, 68). The gold standard test to confirm or exclude allergy is a provocation test, where a dose of the antibiotic is administered and the patient observed for signs of allergy (59, 170). Prior to this, patients typically undergo skin testing (with or without serum specific IgE quantification), which offers additional information on risk level. Skin testing and serum specific IgE testing demonstrate high specificity and positive predictive value, and positive skin tests are generally considered to preclude the use of provocation testing (171). Conversely, skin testing (and serum specific IgE testing) is estimated to have low sensitivity and negative predictive value (171). The likelihood of a positive provocation test after

negative skin testing is thought to be low, estimated in two studies to be around 8% (172, 173).

The pathway detailed above is relatively laborious, time-consuming and expensive – and there are fewer than 140 allergy specialists in the UK to deliver this (84). As a result, testing is effectively inaccessible to most patients with the label. To address this unmet need, novel pathways for penicillin allergy testing have been developed in recent years, as detailed in Chapter 2. These aim to reduce the time and complexity of allergy testing, and to facilitate the involvement of non-allergists in order to increase the pool of healthcare professionals who can deliver testing. Several small, mostly single centre, efficacy studies involving a variety of (non-allergist) healthcare professionals, have been conducted in the UK and beyond. These suggest that up to 65% of patients are suitable for non-allergist delabelling, and that rates of adverse reactions appear to be around 3-4% (174). This is broadly similar to the expected rate of adverse reactions to penicillin in patients who do not have an allergy label (175-177). To date, no published studies involving non-allergists have reported the occurrence of anaphylaxis or death following a provocation test.

Nevertheless, the quality of evidence supporting non-allergist delabelling is low, and its safety and effectiveness remain unproven. Outcome measures such as reduced antimicrobial resistance at the individual or population level, or improved health outcomes over the lifetime of an individual, can be complex to determine and would require data to be collected from large populations over several decades. Whilst some studies have suggested lower healthcare costs from using penicillin, rather than expensive alternative antimicrobials, the cost of delivering the delabelling intervention itself is unknown and overall cost savings cannot be confirmed (107, 112, 178). In addition, the seemingly high level of patient satisfaction in delabelling studies is undermined by the pre-selection of patients motivated to undergo delabelling. Acceptability among other patient groups, in particular ethnic minority groups, remains unknown. The totality of this evidence suggests that while non-allergist delabelling as a routine intervention in the NHS may be beneficial at both the individual and societal level, further research is required to understand how this should be implemented.

The SPACE study aimed to address some these uncertainties and determine whether routine non-allergist delabelling is deliverable in the NHS. I co-led the inception, design and overall delivery of the study with a consultant immunologist working at University of Birmingham, providing direct oversight of the study in Leeds Teaching Hospitals NHS Trust. I co-drafted the manuscript, subsequently published in the Journal of Infection in 2024, and led much of the dissemination work following completion of the study. The study included three workstreams: a feasibility study of non-allergist delivered delabelling; qualitative research to explore views, perceptions and acceptability of the intervention among patients and healthcare providers; and a cost effectiveness analysis. The research was conducted among three distinct populations – acute medical, haematology-oncology, and pre-surgical patients. In this chapter, I detail the conduct and findings of the feasibility study only within the pre-surgical population, since these patients are the focus of my research. This includes a statistical analysis which I performed post-publication, using the final dataset from the study. I have also included summary details of the conduct and outcomes of the qualitative and health economic workstreams, with particular reference to the pre-surgical population, to provide greater depth to the overall findings.

3.2 Study aims and objectives

3.2.1 Aims

This study aimed to determine feasibility of a non-allergist delivered delabelling pathway within routine NHS care, providing key data on proportion of patients able to undergo this intervention in a real-world setting, likely uptake of the intervention, and barriers and enablers to its wider NHS roll-out.

3.2.2 Objectives

- Provide descriptive data on pre-surgical patients with penicillin allergy labels
- Determine the proportion of screened patients eligible to participate
- Determine the length of time to complete each component of the intervention

- Determine the proportion of patients stratified as high or low risk
- Determine the proportion of eligible, low risk patients who are successfully delabelled
- Determine the incidence of all adverse events following challenge testing

3.3 Methods

This multicentre feasibility study was funded by the National Institute for Health and Care Research Health and Social Care Delivery programme (NIHR129069). This funding application was jointly led and secured by myself and Professor Krishna. The study took place between May 2021 - April 2023, in three participating NHS Trusts including University Hospitals Birmingham NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust and Oxford University Hospitals NHS Foundation Trust. Ethics approval from the London Bridge Ethics Committee was secured in July 2021 (REC reference 21/PR/0814, IRAS project ID 293544. See Appendix 8.11.2 for approvals letter), and was prospectively registered in a clinical trial registry (ISRCTN55524365). At each site, the delivery team comprised either research nurses or pharmacists, a medical consultant without prior training in allergy, and an allergy specialist consultant.

3.3.1 Training of healthcare professionals delivering the intervention

All staff members undertaking risk stratification and drug provocation testing, or providing medical supervision for these processes, completed a standardised training package developed by the central study team prior to commencement. This comprised a half day workshop delivered by study PIs, in which the principles of penicillin allergy testing, risk stratification, and provocation testing were outlined. Scenario-based learning was used to support and strengthen this training. See Appendix 3 for brief selection of clinical scenarios used for this training. In Leeds, I delivered this training and supplemented this throughout the study by regularly meetings with the delivery team to discuss queries and difficulties. Other sites provided additional training through different means; for example, the research pharmacists in Birmingham and Oxford gained additional knowledge and experience by attending allergy clinics and observing how specialists took an allergy history. Whilst non-

standardised, these ad-hoc training opportunities allowed us to better understand what future delivery teams might find useful, and how to improve their training.

3.3.2 Public and Patient Involvement and Engagement

The study team worked closely with two groups of members of the public, alongside representatives from Allergy UK (Mrs Amena Warner, Clinical Lead) and the UK Sepsis Trust (Dr Ron Daniels, CEO). An open invitation for recruitment to the PPIE group was hosted on the University of Birmingham website, on the SPACE study twitter account, and 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 each had one PPIE group comprising five members. This was considered sufficient by the study team and the NIHR, so a similar group was not established in Leeds. At each site, local investigators coordinated meetings with their respective PPIE groups and maintained regular contact (five meetings at each site over the course of the study). The membership agreed on terms of reference and received copies of meeting agenda, minutes and ongoing study progress updates and NIHR reports, and study amendment documents. All meetings were conducted via a virtual platform. Our approach throughout the study was aligned with the Guidance for Reporting Involvement of Patient and Public (GRIPP2) guidance/checklist.

The development of patient facing information was informed by prior learning from the PADLES and DALES studies, which I led in 2019 and 2020 respectively. These studies highlighted a lack of awareness among patients and the public around the potential harms of incorrect penicillin allergy labels and the purported benefits of delabelling. Further discussion with our PPIE groups and patients with lived experience of penicillin allergy, led to the creation of posters and patient information leaflets for the study. Posters were displayed in the pre-surgical areas, as well as in primary care settings where possible.

Help was sought from the PPIE groups when recruitment was slow in the early stages of the study, primarily due to the COVID-19 pandemic. It was agreed that recruitment of acute medical patients, who were the most likely to be excluded due to concurrent covid infection, should be stopped. Resources were redirected to the recruitment of pre-surgical and haematology-oncology patients. Strategies to prevent on the day cancellation of provocation testing due to covid infection were discussed and implemented, and included the advance provision of lateral flow tests. The PPIE members were also consulted about the proposed reduction in sample size and supported this. At the end of the study, the PPIE groups and patient-facing organisations helped design our dissemination strategy, and participated in a dissemination event held at the Royal College of Physicians in London, 2024. Lay summary infographics were developed and disseminated through social media and via Allergy UK and Sepsis UK.

3.3.3 Screening, recruitment and consent procedures

Patients were identified through the hospital electronic record and screened for eligibility by the research nurse or pharmacist. Inclusion and exclusion criteria are outlined in Table 20. The screened population was enriched at smaller sites by the inclusion of patients identified by study team members or their colleagues in the perioperative setting.

Table 20: Eligibility criteria for SPACE study, adapted from study screening log

Inclusion criteria	• Age ≥ 18yrs • Label of penicillin allergy in medical records
Exclusion criteria	• Clinically unstable e.g.: respiratory failure, cardiac failure, pre-hepatic encephalopathy • Unable to provide informed consent • History of severe delayed systemic hypersensitivity reaction to penicillin* • Pregnant or breastfeeding • Concomitant COVID19 infection • Underlying psychiatric condition which impacts on ability to give informed consent** • Currently participating in other research or participated in research involving medicinal products, medical devices and/or other interventions in preceding 6 weeks • Currently receiving omalizumab or received in prior 6 months • Currently taking antihistamines and unable to temporarily withdraw use prior to proposed DPC • Deemed unsuitable for any medical reason

* Documented Stevens-Johnson syndrome; toxic epidermal necrolysis, acute exanthematous generalised pustulosis; erythema multiforme; haemolytic anaemia; vasculitis; acute interstitial nephritis

** including severe depression or anxiety; dementia; schizophrenia

Eligible patients were approached by the study team by telephone, provided with study information and invited to participate. Consenting patients were subsequently risk stratified by the research nurse/pharmacist, who completed this process electronically using REDCap, a secure web-based system for data capture. In brief, the risk stratification comprised a series of questions aimed at identifying features in the patient's allergy history suggestive of

previous immediate (type 1) or delayed (type 4) hypersensitivity reactions to a penicillin antibiotic. In addition, the questionnaire identified significant co-morbidities which would preclude drug provocation testing. This process was supplemented by review of the clinical records in primary and/or secondary care, if felt necessary by the research nurse or pharmacist. See Figure 16 for risk stratification proforma, modified from the electronic REDcap survey.

Written informed consent obtained (Yes or No)	
RISK STRATIFICATION	**Yes/No**
Is there a history of type-1 hypersensitivity reaction to penicillin antibiotic? [rash/urticaria, swelling (angioedema), wheeze, throat swelling or symptoms of low blood pressure] ≤1 hour after administration of penicillin/s*]. **If yes, 'HIGH RISK'**	
Description of rash suggests a serious reaction (blistering, painful, desquamating or bruising rash) - stratify - '**If yes, 'HIGH RISK'**	
History of severe asthma or uncontrolled or brittle, severe COPD, or severe impairment in heart function or heart failure or clinically unstable – **If yes, 'HIGH RISK'**	
Previous history suggestive of a serious nonimmediate hypersensitivity reaction to penicillin/s (eg: Steven Johnson Syndrome, Toxic Epidermal Necrolysis, Acute Exanthematous Granulomatous Pustulosis, Erythema Multiforme, Acute Interstitial Nephritis, Haemolysis) – **If yes, 'HIGH RISK'**	
Reaction requiring hospital treatment – **If yes, 'HIGH RISK'**	
History of angioedema occurring <1 hour after taking penicillin/s, as a part of index reaction – **If yes, 'HIGH RISK'**	
No history of previous reaction but avoiding penicillin due to a family history of penicillin allergy – **if yes, 'LOW RISK'**	

Tolerated comoxiclav or augmentin or amoxicillin since original label of 'penicillin allergy' – **if yes, 'LOW RISK'**	
Mild 'benign' rash* ***only*** occurring >1 hour after first dose or during course of therapy – **if yes, 'LOW RISK'**	
Remote (>10 years) reactions without features of an IgE mediated reaction – **if yes, 'LOW RISK'**	
those with an indeterminate history but non-life threatening and did not require hospitalisation – **if yes, 'LOW RISK'**	
Time taken to complete this proforma	
STRATIFICATION (**State 'HIGH RISK' or 'LOW RISK'**)**	
If 'LOW RISK' – discuss with study consultant for approval for a DPC	

Figure 15: Risk stratification proforma used in SPACE (abbreviated for ease)

*Benign rash defined as non-blistering, not painful, non-desquamating, non-bruising

**For HIGH-RISK stratification, at least 1 high-risk criterion should be YES. For LOW-RISK stratification, at least 1 LOW RISK criterion should be YES AND ALL high-risk criteria must be NO.

Patients deemed high-risk were provided with a letter detailing this outcome and the GP was advised to consider referral to a specialist allergy clinic, depending on whether the patient met the NICE clinical guideline for further assessment (see Figure 17 for these criteria).

Patients stratified as low-risk and suitable for a provocation test by the research pharmacist or nurse were then discussed with a medical consultant, who either confirmed suitability or excluded the patient. Specialist advice from the allergy specialist consultant was freely available to the team when required. In Leeds, this specialist advice was provided by me, and was sought for an estimated 25% of patients (data not formally collected).

CRITERIA FOR REFERRAL TO AN ALLERGY SPECIALIST FOR PATIENTS STRATIFIED AS 'HIGH RISK' (At least 1 of the following criteria must be met)

1. An infection-related co-morbidity where penicillin antibiotic/s are deemed important (eg: recurrent urinary tract infection, recurrent skin infection etc.,)
2. Immunodeficiency or immunocompromised state
3. Asplenia or hyposplenism
4. Underlying cancer
5. Chronic respiratory disease (eg: asthma, COPD, bronchiectasis)
6. Diabetes
7. 'multiple antibiotic allergy' label

Figure 16: Criteria for referral to allergy specialist

3.3.4 Drug provocation testing

Low-risk patients were offered a drug provocation test to the penicillin which caused the index reaction, or to amoxicillin where the index drug was unknown. The test took place in a clinical environment with immediate access to resuscitation drugs, equipment, and personnel in case an allergic reaction occurred including anaphylaxis. The provocation test was performed by the research nurse or pharmacist, with the study medical consultant or consultant anaesthetist immediately available on site. See Figure 18 for full details of the conduct of the DPC. In brief, patients received a single, full dose of the antibiotic and observed for one hour. Patients received information on what to do in the event of adverse reactions once they left hospital. Five days after the test, patients were contacted by telephone to check for adverse delayed reactions. The outcome of the test was communicated to the patient and their GP using template letters, and the hospital record was updated.

Conduct of drug provocation test

- Confirmation that no antihistamines taken for previous 3 days
- Urine pregnancy test for female participants of childbearing age
- Written consent confirmed and patient checked for any intercurrent illness
- Baseline heart rate, blood pressure and oxygen saturations recorded
- Single dose of 500mg amoxicillin* administered
- Heart rate, blood pressure and oxygen saturations recorded at 60 minutes, or at any time the patient notices signs or symptoms of possible allergy
- Patient discharged with advice on actions to take if symptoms of non-immediate reaction occur
- 3-day course of 250mg amoxicillin twice daily provided for selected patients**

Figure 17: Conduct of drug provocation test

* If index penicillin known and is different, the index penicillin is administered

**Prolonged course provided for patients in whom the index reaction was non-immediate or unknown

The SPACE study patient pathway is outlined in Figure 19 below, with each component of this detailed in the sections below.

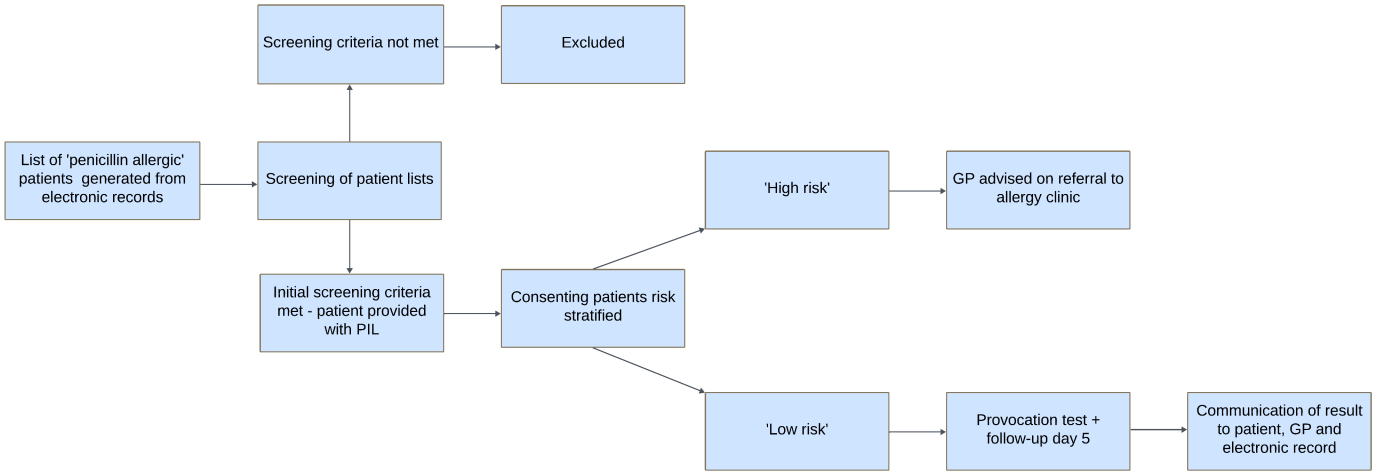


Figure 18: Patient pathway in the SPACE study

3.3.5 Sample size calculation, data handling and statistical analysis

3.3.5.1 Sample size

During study design, a sample size was calculated based on the expected rate of adverse reactions. At the time, the best available evidence suggested a rate of 1% for adverse reactions of any severity. We determined that with a sample size of 375, we would expect to see an adverse event with a probability of 97%. This was based on the standard error of this estimate (assuming binomial distribution) of sqrt (0.01*0.99/375), with 2SD 0.01%. As the study progressed, a decision was made to revise our sample size. A systematic review published after SPACE recruitment had begun, had determined that among 1202 patients undergoing delabelling, none suffered a severe adverse reaction (119). Estimating this rate with 95% confidence interval (+/-3%), a revised sample size of 122 was calculated. This revision was approved by the oversight committees for the study and by the NIHR.

3.3.5.2 Data handling and statistical analysis

Data were entered onto RedCap and held by Leeds Teaching Hospitals NHS Trust. At the end of the study, the complete data set was transferred to Birmingham NHS Trust. A pre-specified

statistical analysis plan was not developed during the original study design, but I developed one in order to perform my own analysis of the surgical population as part of this thesis (see Appendix 4).

3.4 Results

3.4.1 Overall results of screening, recruitment, risk stratification and provocation of pre-surgical patients

See Figure 20 for flow diagram of patients. A total of 992 'penicillin allergic' pre-surgical patients were identified across all three study sites. A total of 277/992 patients were deemed ineligible on screening and did not progress further in the study. See Table 21 for characteristic of all screened patients and Figure 21 for reasons why patients were considered ineligible.

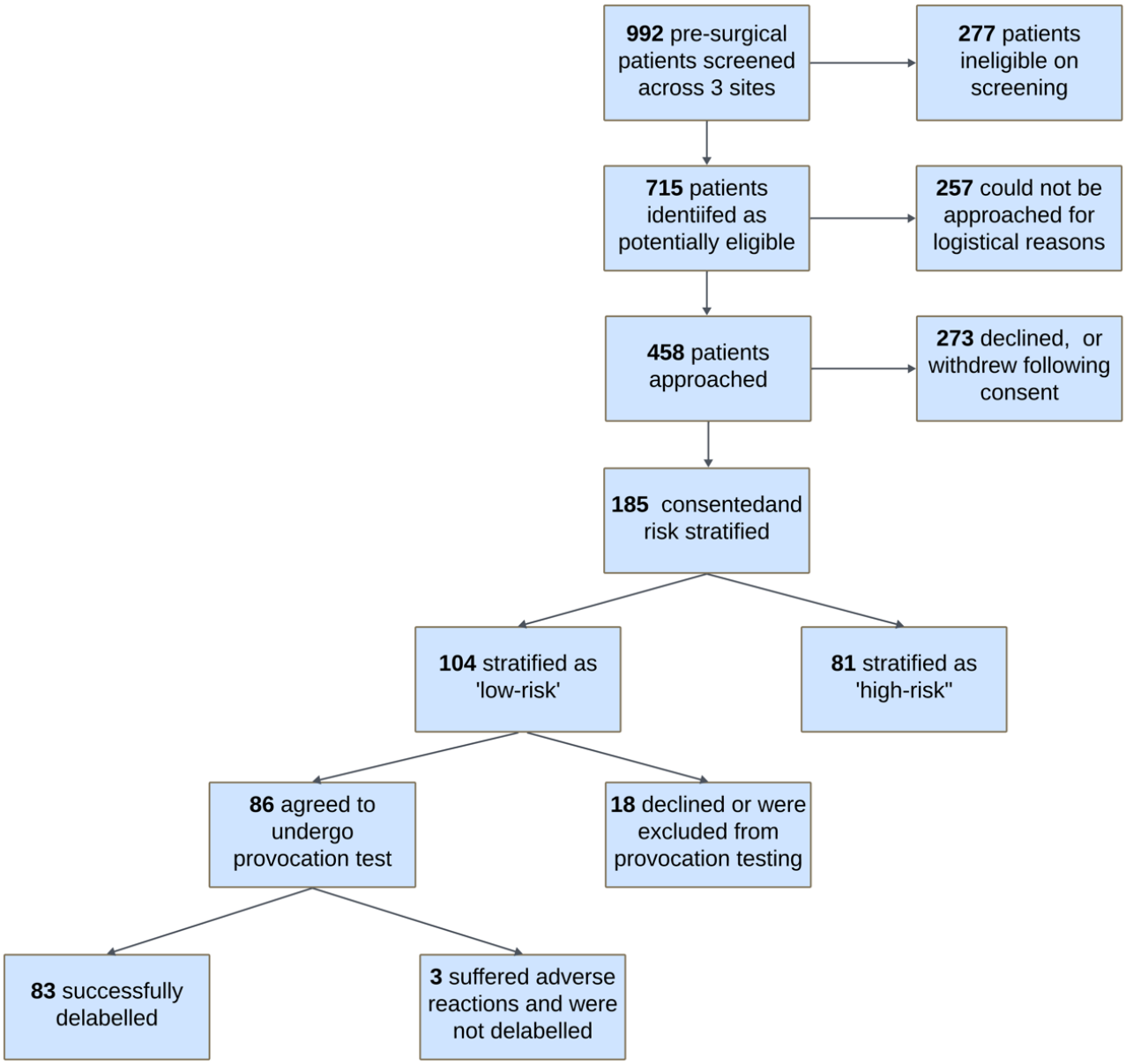


Figure 19: Flowchart of pre-surgical patients in SPACE study

Table 21: Characteristics of all screened pre-surgical patients

	Eligible on screening n=715	**Ineligible on screening n=277**
Sex		
Female	448 (63%)	178 (64%)
Male	267 (37%)	99 (36%)
Age (years)		
18-29	45 (6%)	12 (4%)
30-39	80 (11%)	20 (7%)
40-49	118 (17%)	37 (13%)
50-59	139 (19%)	48 (17%)
60-69	143 (20%)	61(22%)
70-79	137 (19%)	64 (23%)
80-89	49 (7%)	32 (12%)
>90	4 (1%)	3 (1%)
Ethnicity		
White	537 (75%)	214 (77%)
Mixed or multiple ethnic groups	8 (1%)	1 (<1%)
Asian or Asian British	29 (4%)	10 (4%)
Black, African, Caribbean or Black British	11 (2%)	10 (4%)
Other ethnic group	48 (7%)	13 (5%)
Data not available	82 (11%)	29 (10%)

The majority of patients excluded at screening were deemed clinically unstable or were in the category of 'unsuitable for other reason'. See Figure 21. The proportion of screened patients who were eligible was broadly similar across all three study sites.

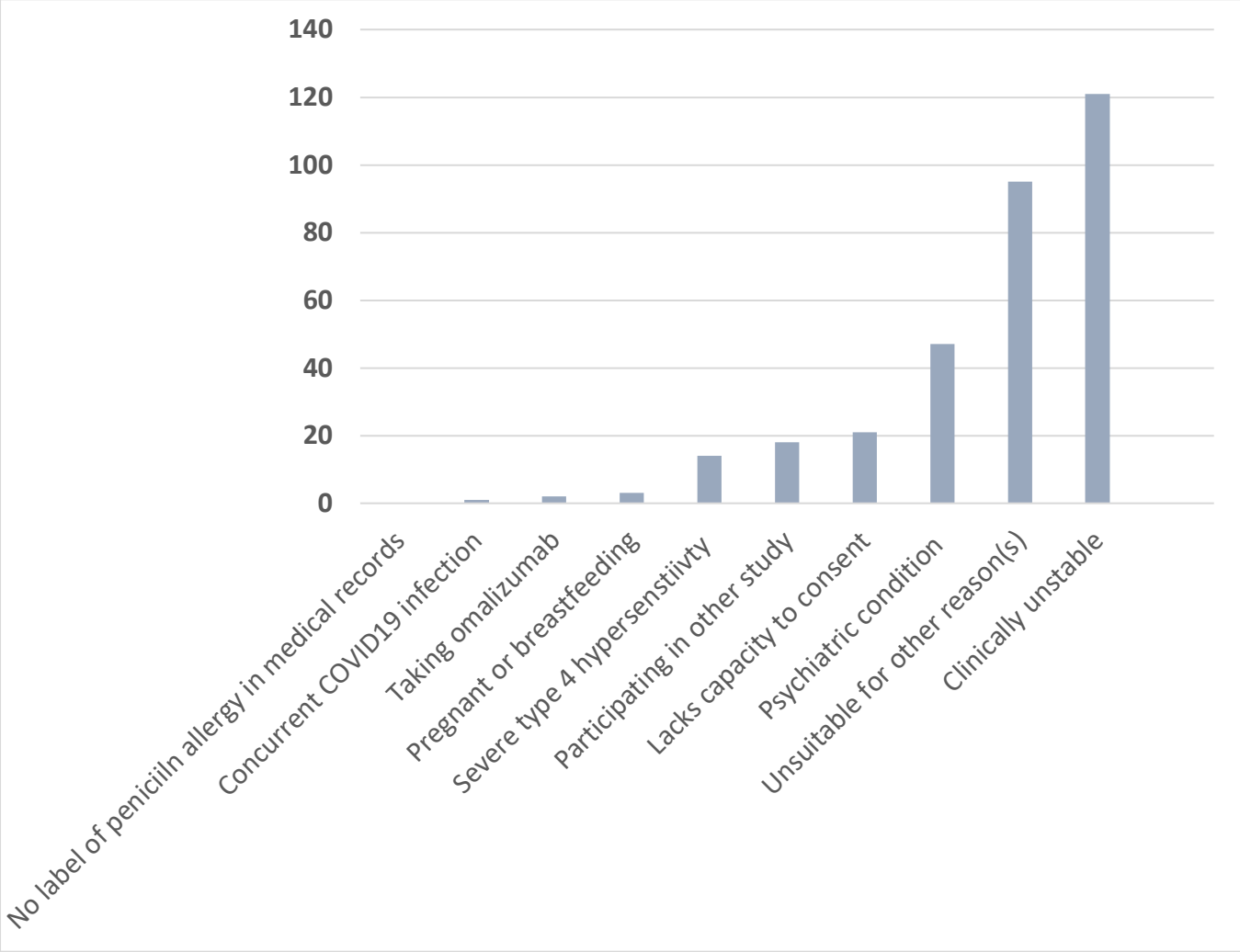


Figure 20: Reasons for ineligibility at screening

3.4.2 Progress of eligible patients through the study

Of 715 eligible patients, only 185 (26%) were subsequently consented and risk stratified. Of the remaining 530, approximately half could not be contacted by the study team and half declined to participate or agreed but later withdrew consent. Reasons for not wishing to participate were not captured during the study. Among 185 risk stratified patients, 104 (56%) were deemed low-risk and invited to undergo a provocation test. For the patients deemed high-risk, a letter was sent to the GP with advice on whether referral to a specialist allergy

clinic would be appropriate. The proportion of patients subsequently referred to clinic and the results of these assessments, were not captured in the study.

Among patients stratified as low-risk, a further 18 later withdrew consent to undergo provocation testing or were excluded on the basis of intercurrent illness on the day of the test. The remaining 86 patients were administered a provocation test, with none suffering any immediate adverse events during testing, but three patients reporting minor, delayed symptoms during the 5-day follow-up period. These patients were considered to have had a positive provocation test and were not delabelled. For the remainder, written confirmation of their delabelling was provided to the patient and their GP.

3.4.3 Data discrepancies between this analysis and the published data

During the analysis of the pre-surgical patient cohort which I conducted for this thesis, I identified a difference in the proportion of pre-surgical patients found to be eligible for the study, compared to figures in the published manuscript in Journal of Infection (179). In my analysis, for which I used the final dataset transferred from Leeds to Birmingham at the end of the study, a total of 715/992 patients met eligibility criteria for the study. However, the original study analysis identified 700/992 patients as eligible. This was subsequently investigated by the study team to ensure the published data were correct. It was concluded that the screening eligibility criteria had been applied slightly differently across sites, with a small number of patients defined as ineligible only after being approached by the study team. Given the very low impact of these differences on the overall findings and conclusions of the study, the study team and sponsor were satisfied that no amendments were required to the manuscript or NIHR final report.

3.5 Other workstreams conducted within SPACE study

The SPACE study comprised three workstreams in total, of which the feasibility study detailed above was one, and the others were a qualitative study among patients and healthcare workers, and an economic evaluation. Both these papers have subsequently been published (113, 180). These publications detail the full methods and findings for each, but below I

present a brief outline of these studies with particular reference to the pre-surgical population.

3.5.1 A qualitative evaluation of the factors affecting implementation and adoption of direct oral penicillin challenge for allergy delabelling

3.5.1.1 Research aims

The aim of this qualitative study was to understand the behaviour, attitudes and acceptability of direct provocation testing among patients, healthcare professionals and NHS managers. Further, we sought to identify the individual contextual and organisational factors which might influence the implementation and adoption of a non-allergist delivered delabelling intervention.

3.5.1.2 Methods

A mixed-methods evaluation was nested within the larger multicentre SPACE study at all three study sites. This comprised patient interviews and healthcare professional focus group discussions.

Patient cohort

Patients who consented to risk stratification in the feasibility study and were found to be low-risk, were subsequently provided with information about the qualitative study and invited to participate in this. Patients were sampled purposively across the three sites, aiming for maximum variation in age, ethnicity and sex. A minimum target of 10 —15 patients was selected per site. Semi-structured individual interviews were conducted with patients in March 2022 by two SPACE researchers, using a topic guide developed a priori which was informed by risk perception theories and drew on broad principles of qualitative methodology (181). See Appendix 5 for topic guide, which was piloted in consultation with the public and patient partners for the SPACE study.

Healthcare professional cohort

Healthcare professionals from a range of backgrounds were invited through emails, poster advertisements and word of mouth, to participate in focus groups. This included allergy specialists, pharmacists, nurses, microbiologists, managers, and clinical commissioners, to ensure as wide a representation of stakeholders as possible. Focus groups for these professionals were held in November 2022. These group discussions were facilitated by a topic guide which drew on relevant domains of the Theoretical Domains Framework (182).

Further focus groups were held at the end of the study. For these, healthcare professionals who had delivered the SPACE study were invited to participate. The remit of these groups was to determine the exact processes for delivery of the study at each site, with discussions built around the template for intervention description and replication framework (183). Broadly, the discussions aimed to elicit the why, what, how and where of intervention delivery at the different sites. See Appendix 6 for topic guide for these focus groups.

Data collection and analysis

Interviews and focus group discussions were audio recorded and transcribed verbatim using a secure online transcription service. Two researchers performed line by line coding of initial transcripts, agreed a codebook and applied this to the remaining data. Thematic analysis of the final codebook was undertaken, using an inductive approach informed by the Theoretical Domains Framework.

3.5.1.3 Summary of results

A total of 43 patients underwent an interview, of which 31 (72%) were pre-surgical patients. All except three participating patients had agreed to undergo a provocation test. Twenty-eight healthcare professionals participated in three focus groups. Themes were divided into those relating to before, during and after phases of the provocation test intervention. Patients reported varying knowledge about penicillin allergy and typically had limited understanding of the potential harms arising from this label, but reported high levels of trust in the safety of

this intervention and felt that the hospital environment provided reassurance when having the test. Nevertheless, some patients who were successfully delabelled reported that they would continue to mention their historic allergy label to healthcare professionals, as a precaution.

The healthcare professionals displayed more nuanced perspectives. Some reported lack of confidence in performing the risk stratification and subsequent provocation test. This was highly influenced by their baseline knowledge and experience in assessing penicillin allergy labels, with some research team members acknowledging very limited prior knowledge. The need for easy access to allergy specialists was seen as critical to the safety and success of delabelling. Of particular note, they described the extensive changes required to clinical behaviours, systems and routine practice, for delabelling to be implemented more widely. This included organisational-level and national frameworks to support delabelling. There were important contextual factors which affected implementation at each site, which included the greater experience of some of the research team (including some with post-graduate level experience of penicillin allergy testing).

3.5.1.4 Conclusions

The patients included within this study were predominantly from the pre-surgical arm of the study, and the results are therefore most pertinent to this population. We found that patients have high trust in the delabelling process but that healthcare professionals perceive an unmet need for appropriate governance frameworks, organisational support, and risk management. Whilst the healthcare worker findings are likely to be generalisable, our patient cohort only represents those who were keen to engage in the study and undergo a provocation test. This substantially limits the generalisability ('transferability') and utility of our findings.

3.5.2 Health economic analysis of SPACE

3.5.2.1 Background and rationale

As detailed in the introductory chapter, the economic benefits of delabelling have yet to be fully elucidated. Some research has identified cost saving from the increased use of penicillin

and reduced consumption of alternative antibiotics and antibiotics overall, and the lifetime cost benefits of this have been estimated (107, 108, 110, 112). There is also a limited amount of evidence to suggest that other healthcare costs such as emergency or outpatient department visits are reduced following delabelling (109). However, this picture is incomplete. Our understanding of the potential cost benefits is limited partly by a lack of long-term data demonstrating reduced incidence of nosocomial infections and incidence of multi-resistant infections, which would require longitudinal, population-level studies over several years. Further, the cost of delabelling has not been explored in detail. Work from the US has shown that the cost of the provocation test is offset by the savings in the cost of future antibiotic use, but these studies are based on the cost of a single provocation test rather than the complete pathway required to enable this intervention. Furthermore, the costs of this pathway may differ by the clinical setting and personnel involved. SPACE aimed to determine the true cost of delabelling across all the study settings.

3.5.2.2 Methods

In brief, the intervention pathway for the study was mapped at each site and compared against the usual care pathway (ie no testing, treat as usual). The key data used to inform this included:

1. Cost of staff attending and delivering study training (assumed to be valid for 2 years)
2. Time taken to screen patients
3. Time taken for the provocation test
4. Grade and unit time cost of staff member performing screening and provocation test
5. Unit cost of time provided by study consultant during provocation test
6. Cost of antibiotic use for provocation test
7. Estimated cost of alternative antibiotic for surgical prophylaxis (which varied by procedure)

3.5.2.3 Summary of results

We determined that the anticipated cost for delivery of the provocation test differed at each site, estimated at £577 (95%CI 370-633) in Leeds, £715 (582-811) in Oxford, and £1280 (1027-1608) in Birmingham. We also found that Leeds, where the study was delivered by nurses rather than pharmacists, had the lowest cost per provocation test in all settings. Among 26 surgical patients who were delabelled prior to surgery, the mean difference between the cost of antibiotic therapy recommended for their operations with and without a penicillin allergy label (according to the local hospital guideline) was -£1.95, or -£0.44 per de-labelled patient.

3.5.2.4 Conclusions

Our data suggest that delabelling of surgical patients is likely to yield the greatest cost-effectiveness, especially if nurses are employed to conduct the intervention rather than pharmacists. However, our analysis has several limitations. Firstly, we only costed for consultant time on the occasions where this was specifically sought and documented. In reality, the consultant was required to be on site and immediately available throughout each provocation test in case of adverse reactions, and this cost is likely to be substantially underestimated. Immediate availability precludes the consultant undertaking planned clinical activity elsewhere and this supervisory role would need to be factored into job planning as a dedicated activity. Conversely, our figures might be artificially inflated by the research framework in which the study was delivered, with some of the study activities absorbed into routine care or conducted by less experienced staff in a future model. Lastly, our analysis could not accurately account for the long-term cost savings which might be realised through delabelling.

3.5.2.5 Summary

We found that the cost of delabelling is greater than previously reported, when accounting for all aspects of the delabelling pathway. Surgical patients appear to be the cohort with the lowest overall cost of delivery, particularly when compared to medical in-patients. The true cost, and potential cost savings, of implementation remain unknown.

3.6 Discussion

This was the first multicentre, prospective feasibility study of non-allergist delabelling in an unselected population of pre-surgical patients with a penicillin allergy label. The key findings were that overall uptake of the intervention was low, with only 8% of all potentially eligible patients eventually delabelled. compared to previous studies suggesting that at least 65% of penicillin-allergic patients can be delabelled using this intervention. Compared to other patients within the study, the surgical population had the greatest likelihood of progressing through the study. The proportion of low-risk allergy histories was aligned with previous work, at approximately half of consenting patients stratified as low risk.

We identified important barriers to delabelling, and key learning points for the future development of the intervention. These are discussed further in the sections below, with inclusion of relevant qualitative research findings from the study.

Fewer than half of patients approached by the study team consented to participate. A further 18% of eligible patients who initially consented to participate and were stratified as low risk, subsequently declined to undergo provocation testing. The reasons for declining participation were not captured in this study. Substantial work is needed to elucidate these reasons and understand how uptake can be improved.

3.6.1 Barriers to uptake of the intervention

Multiple barriers contributed to low uptake in this study. Whilst some of these relate specifically to the covid pandemic, many reflect 'real-world' difficulties which are likely to affect any future implementation of the intervention. Some of these are easier to address than others. Cognitive impairment, underlying psychiatric disturbance, and long-term health conditions which preclude provocation testing in the non-specialist setting, accounted for a large proportion of exclusions. As the population increases in age and comorbidity, the presence of such factors is likely to increase and may limit the clinical effectiveness of a delabelling intervention. Recognising that these groups should not be precluded from high quality healthcare simply because of a diagnosis of poor mental health or cognitive impairment, a more inclusive approach should be taken in future research. Other barriers

included logistical difficulties in contacting patients at home, such as holding incorrect telephone numbers, patient unwillingness to answer calls from unknown numbers, and simple mismatch of research team and patient availabilities. Many of these issues might be addressed using text messaging via trusted sources, as is routine in other areas of healthcare. Future interventions could use an alert on the patient record to prompt home-team clinicians to discuss delabelling with the patient, to increase the impact of this message. Greater awareness of the benefits of penicillin allergy delabelling at a population level, may also improve future uptake, since it was noted that most patients were unaware of the potential harms associated with the label.

3.6.2 Intervention fidelity and contextual differences between sites

There were notable differences in the delivery of the intervention between the three sites. At the smaller sites, information about the study could be disseminated more effectively and enrichment of the eligible population occurred through the contribution of non-study colleagues who actively sought out potentially eligible patients. In larger sites, this 'word of mouth' effect was less effective and such enrichment did not occur.

A further contextual difference existed in the training requirements of staff delivering the intervention. The research pharmacists involved in the study typically had pre-existing knowledge around penicillin allergy and delabelling prior to the study, and some even had previous experience of delabelling patients. This knowledge was further enriched for some individuals throughout the study by working alongside the allergy specialist nurses in the delabelling clinic, and by shadowing specialists in drug allergy clinics. The research nurses, by contrast, had no prior knowledge or experience of penicillin, and received minimal or no additional training during the study. At the site with research nurses, expert allergy advice on risk stratification was sought for a substantial proportion of the patients, whilst other sites reported that this was rarely required. Quantitative data on this issue were not captured in the study, but in the qualitative workstream a clear theme emerged that the nurses found it difficult to risk stratify patients and lacked confidence in doing so. This suggests that taking an accurate allergy history is likely to require training and experience. As the study

progressed, it was clear that staff gained greater confidence in the process and were more able to risk stratify independently. Future research needs to focus on understanding the training needs and levels of required supervision for any non-allergist delivered pathway. Whilst these elements of the study were not strongly emphasised in the published paper, they are key to understanding whether non-allergist delabelling can be rolled out at scale.

3.7 Key messages from SPACE

The data suggest that non-allergist delivered delabelling is likely to be possible, but that further implementation research is needed to improve its effectiveness. The pre-surgical population had the greatest proportion of eligible, consenting patients and were found to have the lowest cost per provocation test, so may also be the most cost-effective group to target for future interventions. This is also a group which can be targeted with relative ease to offer interventions which aim to improve surgical outcomes. Smoking cessation, correction of iron deficiency anaemia and physical 'pre-habilitation' to reduce frailty are already offered routinely as part of surgical preparation, and widely accepted by patients and staff to be beneficial for both the individual and the healthcare system. Penicillin allergy delabelling arguably also belongs in this space, and could benefit from the existing governance structures and processes. Future research needs are outlined in the concluding chapter of this thesis.

4 PASSPORT: Penicillin allergy risk stratification tool for use by non-allergists in the perioperative setting: an agreement study

4.1 Background and rationale

As detailed in Chapters 1 and 2, a substantial proportion of all patients carry a label of penicillin allergy. This includes an estimated 6% of the overall UK population and estimated 12% of the UK surgical population (92, 97, 98, 170). Most labels are incorrect when tested, erroneously applied when patients experience side-effects such as nausea, because of a family history of penicillin allergy, or for other reasons (119, 171, 174) . The label is associated with an increased incidence of infections with resistant organisms, including methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile* and vancomycin-resistant enterococcus, as well as increased wound infections, treatment failure, longer hospital stays, more frequent admissions to critical care, and increased mortality (2, 4, 97, 99, 101). The use of broad-spectrum alternative antimicrobials contributes to antimicrobial resistance, a serious threat to global health (184, 185).

Testing and removal of the label ('delabelling') leads to increased use of penicillin and reduced overall antibiotic consumption (111, 112, 116, 186). The current standard of care for testing in the UK and beyond is for an allergy specialist to perform skin testing followed, when negative, by a provocation test. This is a time-consuming and relatively expensive process. In recent years, an accumulating body of evidence demonstrates that in patients whose index reaction is low-risk for genuine allergy, skin testing can be omitted, and the patient offered a 'direct' provocation test to confirm tolerance. This appears to be safe, with an incidence of adverse reactions similar to the baseline incidence of adverse reactions seen in all individuals exposed to penicillin (174). However, a critical shortage of allergy specialists means testing is inaccessible to most patients (85, 89, 187).

To address this unmet need, novel delabelling pathways for use by healthcare professionals without formal allergy training have been developed. Central to these is the use of risk stratification tools to allow non-allergists to identify low-risk patients suitable for a penicillin challenge test (115-117, 119-122, 174, 179, 186). This approach is widely reported to be safe and effective (116, 119-121, 179). However, the evidence for this is not robust and warrants

further examination. Most of the published work involves small, single centre cohorts, with substantial variation and potential bias in patient selection, as well as varying degrees of specialist allergy involvement during the delabelling process. Rather than making it easy for non-allergists to identify low-risk patients, emerging evidence suggests that non-allergists lack confidence in this process and have important knowledge gaps about allergy which limit the use of these tools (92, 180, 188). These were some of the key findings from the SPACE study (Chapter 4), in which several non-allergist team members reported difficulty in performing risk stratification and described an unmet for allergy training. It became clear in at least one study site (data not formally captured) that specialist advice from allergists was frequently required for risk stratification decisions, and on at least two occasions, high-risk patients were incorrectly designated as low-risk by the study team. These errors were identified before provocation tests were performed due to the study design, but in a routine clinical pathway might not be detected. These findings were not fully captured in the study, yet are interesting and relevant in terms of future implementation research.

Before non-allergist delabelling pathways are introduced into the NHS or elsewhere, it is critically important to ensure these are informed by robust, reliable data. I believe there are several aspects to these pathways which warrant more careful scrutiny, with risk stratification of the allergy history the most fundamental. The PASSPORT study was developed with the aim of determining the level of agreement between allergists and non-allergists when using a risk stratification tool among 'penicillin allergic' surgical patients, and exploring the decision-making process among non-allergists.

4.2 Aims and objectives

4.2.1 Aims

The overarching aim of this study was to determine the level of agreement between allergists and non-allergists when using the risk stratification tool, providing data to inform our understanding of the potential clinical effectiveness and safety of the tool, and to guide development of its future iterations.

4.2.2 Objectives

These were to:

- Determine the level of agreement between allergists and non-allergists
- Determine the reasons for disagreement and identify questions within the tool where potentially harmful disagreement occurred
- Determine barriers to accurate risk stratification by non-allergists
- Provide qualitative data on user experience of the tool and how this impacts its clinical effectiveness and safety

4.3 Methods

4.3.1 Study design

PASSPORT was a two-centre study conducted at Leeds Teaching Hospitals NHS Trust and Barts Teaching Hospitals NHS Trust. Regulatory approvals were obtained in 2022 (HRA and HCRW; REC reference 22/NW/0174. See Appendix 8.11.3 for approvals letter). Recruitment ran from May 2023 to May 2024.

4.3.2 Patient participants: recruitment process, inclusion and exclusion criteria

Adult patients aged 18 years or over, with a label of penicillin allergy, and who were awaiting any type of surgery were considered eligible. The electronic records of patients on surgical waiting lists were screened at both sites to identify eligible patients, and an information leaflet was sent out at least one week prior to contacting these patients by telephone. Patients who agreed to participate provided formal written consent to be interviewed and for the interviews to be recorded. Exclusion criteria included unwillingness to participate, being unable to consent, or being pregnant. Pregnant patients were excluded, to mirror the eligibility criteria of future interventional studies in which patients would be offered a penicillin challenge test.

4.3.3 Healthcare professional participants: recruitment process, inclusion and exclusion criteria

Consultants specialised in allergy medicine (allergists and immunologists) and non-allergists working in the perioperative setting (consultant anaesthetists and nurses) were sent emails and information leaflets about the study and invited to participate. There were no exclusion criteria. All participating healthcare professionals provided written consent, and underwent a two-hour training session, which I delivered, on how to use the risk stratification tool.

4.3.4 Risk stratification tool

The tool used in this study was adapted from the 2022 British Society of Allergy and Clinical Immunology guideline for non-allergist penicillin allergy delabelling (125). This guideline (for which I led the writing group) defines which patients can be considered 'low-risk allergy history and suitable for a direct challenge test by a non-allergist'. The guideline was developed following a systematic review and subsequent Delphi consensus process, conducted among practising adult allergy specialists in the UK. The guideline was endorsed by multiple national stakeholder bodies including the Royal Colleges of Physicians, Pathologists and Anaesthetists, British Society of Allergy and Clinical Immunology and Clinical Immunology Professional network of the British Society for Immunology. The guideline therefore represents the broadest possible consensus in the current literature. The tool used in the PASSPORT study was beta tested by non-allergy members of the research team to confirm ease of use, but was not formally validated prior to use in this study. See Appendix 7.

In brief, part A of the tool aims to identify the index penicillin which caused the reaction; part B identifies the presence of any high-risk features in the allergy or medical history which would preclude direct challenge testing by a non-allergist; and part C defines which specific low-risk features the patient has suffered in their index reaction. The final section asks users to categorise the patient into: 'safe for a direct challenge test'; 'unsafe for a direct challenge test'; or 'uncertain - patient should not have a challenge test without further discussion with an allergy specialist'. Users were instructed that if any answers in part B were 'yes', the patient was unsuitable for a challenge, but that if all questions in part B were 'no' and only part C had 'yes' answers, the patient was suitable for challenge. The uncertain category was available for

patients in whom the user could not assess questions in parts B or C with confidence. Users were asked to answer every question within the tool and encouraged to provide free text to explain any difficulties or uncertainty they experienced.

4.3.5 Risk stratification interviews

Patients underwent two risk stratification interviews, one with an allergist (considered the gold standard) and one with a non-allergist. A risk stratification tool was completed for each interview. The order of interviews was determined by computer-generated random allocation, to minimise potential bias from improved patient recall of the allergy history following discussion with an allergy specialist. Suitability was dependent on both a low-risk allergy history and the absence of significant comorbidity precluding administration of a penicillin challenge test (for example, severe asthma). Interviews were conducted by telephone or virtual platform (e.g. Zoom) and were recorded where patients consented to this. Recordings were transcribed verbatim using a secure, online transcription service. There was no further patient contact once interviews were completed.

4.3.6 Sample size and statistical analysis

We calculated that a sample size of 74 would be required to determine the level of agreement using the Cohen kappa statistic, based on a minimum acceptable kappa of 0.6, with a significance level of 0.05 and power of 80%. This assumed that the proportion of patients would be assessed as 'unsuitable' by the allergist would be 25% based on previous research (189, 190).

Following a pre-agreed analysis plan, the level of agreement between the allergist risk stratification outcome and the non-allergist outcome was determined using Cohen's kappa statistic. Greater weight was applied where patients were categorised as 'unsuitable' (or 'uncertain') by the allergist but 'suitable' by the non-allergist, since this represents potentially harmful misclassification. To account for potential bias among individual healthcare professionals and the low prevalence of genuinely high-risk allergy histories, a prevalence and

bias-adjusted kappa score (PABAK) was also calculated. We followed the STARD guideline for reporting of our findings (191). STATA v17.0 was used for the analyses.

4.4 Results

A total of 139 patients were recruited, of whom 101 completed both interviews. Their median age was 53 years (19 – 86), the majority (72/101, 71%) were women and White British (82/101, 81%). See Table 22 for patient characteristics and Figure 22 for study flow diagram. Eleven healthcare professionals were recruited, comprising six consultant anaesthetists, two perioperative research nurses, and three consultant allergists or immunologists.

Table 22. Characteristics of PASSPORT participants

Characteristic	Frequency, n (%)
Age (years; range)	
18-25	3 (3%)
26-45	34 (34%)
46-65	37 (37%)
66-85	26 (26%)
>85	1(1%)
Sex	
Male	29 (29%)
Female	72 (72%)
Ethnicity	
White British	82 (82%)
Asian Bangladeshi, Indian, other Asian	5 (5%)
Black, African or Caribbean	3 (3%)
Other White or unknown	11 (11%)

The allergist and non-allergist assessments were concordant for 63 (62%) patients (Table 23). For a further 29% (31/101), there was a non-harmful misclassification by the non-allergist, predominantly representing an over-cautious approach in which a patient deemed suitable by the allergist was deemed unsuitable (or uncertain) by the non-allergist. However, for nine patients (9%), the non-allergist was less cautious than the allergist. Of these, seven (7%) were potentially harmful, with the allergist assessment being unsuitable or uncertain, but the non-allergist assessment being suitable.

Using an unweighted Cohen's kappa score, the inter-rater agreement was determined to be moderate (0.43, 95% CI: 0.30–0.57). Weighted Cohen's kappa score was also moderate (0.47 (95% CI: 0.27–0.67). When adjusted for potential bias among individual professionals and the potential effect of a low prevalence of genuine allergy using the PABAK score (prevalence and bias kappa), inter-rater reliability was determined to be poor at 0.25 (95% CI: 0.06-0.44). Of note, there were eight patients where the assessments agreed, but there was nevertheless a difference in the categorisation of allergy risk. For example, the allergist might assess the patient as unsuitable because of a high-risk allergy history, while the non-allergist incorrectly allocated the allergy history as low-risk but deemed the patient unsuitable because of severe medical comorbidity.

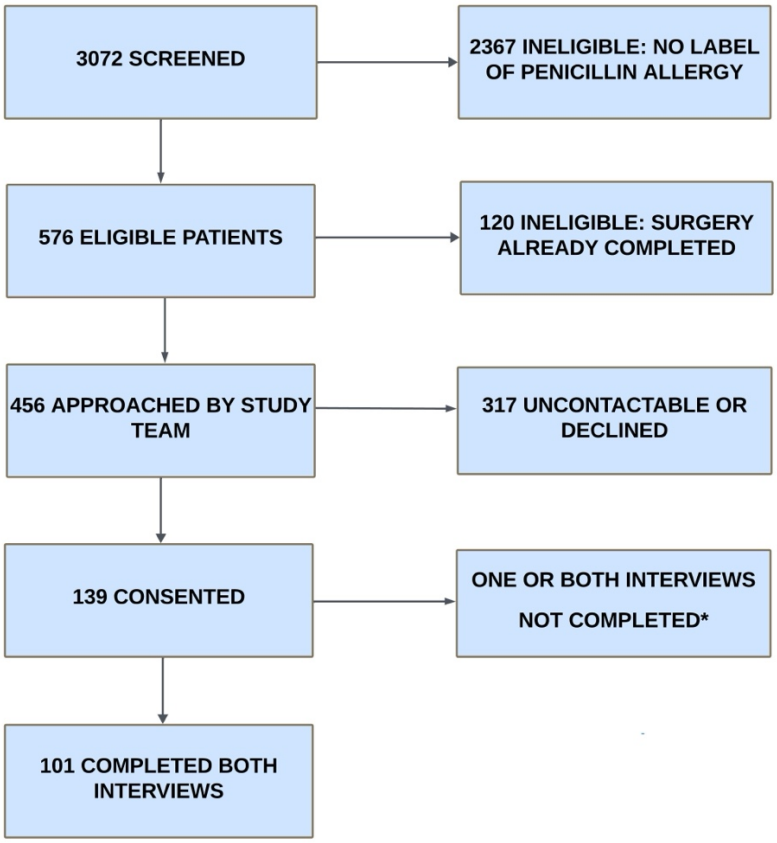


Figure 21: PASSPORT patient flow diagram

** Only 1 interview completed prior to surgery (18); surgery cancelled (1); target sample size already met (2); surgery proceeded before any interviews organised (8); withdrew after consent (9).*

Table 23: Outcomes recorded by allergists and non-allergists

ALLERGIST OUTCOME	NON-ALLERGIST OUTCOME				
		Suitable	*Uncertain*	*Unsuitable*	**Total**
	Suitable	27	15	7	49
	Uncertain	5	11	7	23
	Unsuitable	2	2	25	29
	Total	34	28	39	101

Red indicates a potentially dangerous misclassification; amber indicates an overcautious but non-harmful misclassification; green indicated agreement between healthcare professionals.

Inter-rater agreement was highest when the allergy history was at the extremes of risk (very low or very high). For example, gastrointestinal upset (>80% inter-rater agreement), family history of penicillin allergy (95% inter-rater agreement), anaphylaxis (92% inter-rater agreement) and collapse (94% inter-rater agreement). See Appendix 8 for agreement levels for all questions. The symptom which non-allergists most frequently miscategorised was rash. This is one of the most commonly reported symptoms of penicillin allergy. Of four questions related to rash, two of these ('urticaria within two hours of taking penicillin', and 'rash without blistering or itching') scored the lowest inter-rater agreement of any question in the tool (62% and 64% respectively).

4.5 Discussion

The principal finding of this study was that when the risk stratification tool was used by healthcare professionals without formal allergy training, there was poor agreement with the assessment made by an allergist using the same tool. Most errors represented an over-cautious, but safe approach by non-allergists. However, potentially harmful errors also occurred. The extent of disagreement is under-estimated by the headline PAPAK score, since additional errors were made in risk stratification which were obscured when patients also reported significant co-morbidity, meaning the patient was excluded anyway. A history of

rash was the most difficult for non-allergists to interpret and correctly categorise. Histories which were clearly low-risk histories, such as family history of penicillin allergy, or clearly high-risk, such as anaphylaxis, were relatively easy for non-allergists to categorise.

Several risk stratification tools designed for use by non-allergists are described in the literature, some of which are included within national guidelines for management of patients with penicillin allergy labels (192-194). Such tools are widely accepted to provide good diagnostic accuracy, but this has not yet been conclusively proven. A recent systematic review and meta-analysis of studies in which non-allergists performed risk stratification as part of a delabelling intervention, determined a 1% incidence of adverse events among 5019 patients, none severe or fatal (121). This is broadly similar to the baseline incidence of adverse events for all patients exposed to penicillin (177). However, substantial heterogeneity in these studies means their findings might not inform our understanding of non-allergist delabelling through direct challenge testing, or may be unreliable in other ways. Several studies incorporated skin testing to risk stratify patients rather than stratification based on history alone, with patients observed to have positive skin tests excluded from subsequent challenge testing (195-197). Therefore, the cohort undergoing challenge testing were already selected to be at low-risk of true allergy. In many of the studies, risk stratification and challenge testing was performed by healthcare professionals with substantial expertise in allergy, even if there primary qualification was not in allergy (115, 120, 190, 198, 199). This fundamentally undermines the argument that healthcare professionals without allergy training can perform delabelling. Also undermining this argument, several studies examined the accuracy of risk stratification by non-allergists among patients already confirmed to be low-risk following completion of specialist allergy testing (195, 200). Furthermore, the reportedly high negative predictive value of risk stratification tools used by non-allergists, is based on using the uneventful administration of a single challenge dose as a surrogate marker for accuracy of the initial risk stratification (179, 192, 193, 201, 202). Given the low incidence of anaphylaxis following penicillin administration, estimated at between 1:124,000 and 1:255,000, this assumption is fundamentally flawed (203).

To date, there is limited research specifically examining the accuracy of non-allergist risk stratification. In one study, retrospective risk stratification of the allergy history of 181

pregnant patients was performed using three different stratification tools, and compared to the results of formal testing by an allergy specialist (201). Of 181 patients, 176 were found not to be allergic following specialist assessment, but only 60-88% of these were correctly identified as 'low-risk' by the risk stratification tools and seven patients were incorrectly diagnosed as low-risk. In another study, clinical vignettes of allergy histories were risk stratified by 400 non-allergist healthcare professionals using a stratification tool, and these results compared to risk stratification without use of the tool (204). Use of the tool improved accuracy, but up to 28% of participants made major errors. A stratification tool for use by patients themselves, demonstrated moderate accuracy when compared to specialist assessment, with an interclass correlation of 0.618 ($p < 0.001$), although 6% of patients incorrectly categorised themselves as low-risk (205).

This study provides novel, prospective data describing the level of agreement between allergists and non-allergists when risk assessing surgical patients labelled as penicillin-allergic. Analysis of the answers to specific questions within the tool allowed the identification of specific knowledge gaps and uncertainties among participating non-allergists. This data will inform strategies to improve accuracy of the tool in the hands of non-allergists through iterative modification and retesting. For example, additional questions about 'rash' histories might facilitate more accurate categorisation of these, which could be further facilitated by the use of pictures of different rashes to assist both the patient and the non-allergist. Specific guidance on when to seek advice from an allergist might also improve safety.

4.5.1 Strengths and limitations

One of the key strengths of this study was the inclusion of an entirely unselected patient population. This means the results are reflective of 'real-world' practice and of the types of patients likely to be encountered in any future implementation trial. Recruitment across two sites further strengthens the generalisability of the findings. The results also allow us to determine unequivocally, and perhaps for the first time in this patient group, the accuracy of the tool when used by non-allergists without any specialist allergy input for advice or guidance.

Nevertheless, the small sample size, although greater than required to achieve statistical significance, reduces the generalisability of the findings. This is further limited by a lack of

ethnic diversity in the study cohort. Patient information leaflets in a variety of non-English languages were available but none were requested. Although data were not formally collected, it also became clear as the study progressed that most patients had a reasonable degree of health literacy, and were therefore not fully representative of the wider population. It is not clear why recruitment among patients from other ethnic and health literacy groups was so poor, but this represents a major unmet research need and is discussed later in the thesis.

In addition to limited patient diversity, the small number of participating healthcare professionals means that the results may not be reflective of others, with differing levels of experience, background knowledge and confidence. This was a feature of the SPACE study, reported in Chapter 3, in which we found that pharmacists generally had greater knowledge and experience than nurses, translating to greater confidence when risk stratifying patients. Lastly, a substantial limitation to this study is that the 'gold standard' allergy assessment was itself noted to be inconsistent. Important discrepancies were identified between the allergists, in terms of where they set risk thresholds and what they considered a low-risk history – despite the relatively narrow definition provided within the tool. This reflects the lack of well-established parameters for defining 'low-risk and suitable for a challenge test' and the degree of interpersonal variability in interpretation, and is an area which should be addressed before widespread implementation of delabelling. This is discussed further in the concluding chapter.

4.5.2 Conclusion

In this study, a risk stratification tool used by healthcare professionals without formal allergy training demonstrated poor diagnostic agreement when compared to assessment by an expert allergist. The findings suggest that the de-labelling tool would be both ineffective and unsafe for routine use. Further research is needed to determine whether modification of the tool and delivery of allergy training for non-allergists, would improve accuracy and safety. A definition of 'low-risk and suitable for a penicillin challenge' should be universally agreed, in order to meaningfully compare the outcomes of future agreement studies. Larger and more

inclusive patient cohorts must be included in future research, as discussed in more detail in the concluding chapter.

5 PASSPORT process evaluation: understanding the performance of a risk stratification tool used by non-allergists

5.1 Background and rationale

5.1.1 Summary of PASSPORT findings

In Chapter 4, I presented the PASSPORT agreement study. This examined inter-rater agreement between allergists and non-allergists when using a risk stratification tool to determine whether pre-surgical patients labelled 'penicillin allergic' were suitable for a direct provocation test. The study demonstrated low inter-rater reliability, with a prevalence and bias adjusted kappa score of 0.25 [95% CI:0.06-0.44]. Most of the incorrect classifications represented an over-cautious approach by non-allergists (the allergist classified the patient as suitable, but the non-allergists classified them as unsuitable or uncertain), but a minority (7%, 7/101) of patients were incorrectly categorised as suitable when the allergist categorised them as unsuitable. These data suggests that the tool would be both clinically ineffective and unsafe, if used in within a delabelling intervention. A large proportion of patients would be unnecessarily excluded from a challenge test, whilst some high-risk patients would be exposed to potential harm from a challenge. Further analysis revealed that certain symptoms were particularly difficult for non-allergists to interpret and categorise; mostly these related to rashes experienced by the patient. The overall extent of disagreement was underestimated by the overall PABAK score, because a cohort of patients categorised by the non-allergist as having a low-risk allergy history but with co-morbidity which precluded challenge testing, were considered to have high-risk allergy histories by the allergist. For these patients, the misclassification of allergy risk was therefore obscured by the confounding factor of medical co-morbidity, leading to falsely reassuring agreement between assessments.

5.1.2 Why was a process evaluation needed?

The findings above tell us that the tool performs poorly in the hands of non-allergists, but does not explain the 'why'. Much more granular data are needed about the process of

decision-making by non-allergists and the pre-existing knowledge which informs this, and describing how they deal with uncertainty. There are few studies examining the non-allergist perspective on risk stratification, or their experience of using risk stratification tools. Many of the studies of non-allergist risk stratification included patients already pre-selected as low-risk following assessment by allergy specialists, or with substantial oversight by allergists (115, 121, 190, 201). This limits our understanding of how the tool performs in 'real world' settings and precludes their meaningful adaptation for use in future interventional studies.

5.2 Aims and objectives

5.2.1 Aims

The process evaluation in PASSPORT aimed to explore all these critical aspects of non-allergist risk stratification, gaining detailed understanding of the process of non-allergist decision-making, user experience of the tool, and barriers and enablers to its use. Ultimately, my aim was to provide data which would inform modifications of the tool designed to improve its performance, accuracy and reliability when used by non-allergists.

5.3 Methods

5.3.1 Study design, participants, inclusion and exclusion criteria of main PASSPORT study

A pre-planned process evaluation was embedded within the PASSPORT study. The full methods for the PASSPORT study are detailed in Chapter 5 but in brief, this was a two-centre study conducted at Leeds Teaching Hospitals NHS Trust and Barts Teaching Hospitals NHS Trust. Regulatory approvals were obtained in 2022 (HRA and HCRW; REC reference 22/NW/0174. See Appendix 8.11.3 for approvals letter). Recruitment ran from May 2023 to May 2024. Patient inclusion criteria were age $\geq$ 18 years, awaiting planned surgery (of any type), and labelled as penicillin allergic. Exclusion criteria were unwillingness or inability to consent, and pregnancy. Consenting patients underwent two risk stratification interviews, one with an allergist and one with a non-allergist, which were recorded where possible. The order of interviews was determined by a computer-generated random sequence.

Healthcare professional participants included consultants specialised in allergy medicine (allergists and immunologists) and non-allergists working in the perioperative setting (consultant anaesthetists and nurses). They provided consent to participate in the study, (including recording of their interviews with patients) and to undertake interviews or focus groups at the end of the study. Consent included the use of anonymised illustrative quotes in future publications.

5.3.2 Data sources for process evaluation

Two data sources were used for the evaluation.

I. *Patient/healthcare professional risk stratification interviews*. Two data collection forms were completed for each patient; one from the interview with an allergist and one from the interview with the non-allergist. Where audio or video recording of the interviews had been performed, these were transcribed verbatim using a secure online transcription service (Hightail transcription services(206)).

II. *Interviews and focus groups with healthcare professionals*. Participating healthcare professionals were invited to undergo semi-structured interviews or (if more convenient) a focus group session at the end of the study. Only healthcare professionals who had completed at least four patient interviews were invited to participate, to ensure the experiences of those who had used the tool most frequently were captured. To mitigate the risk of non-allergists being reluctant to share a real or perceived lack of allergy knowledge, groups comprised either allergists or non-allergists and were not mixed. A topic guide was used during both the interviews and focus groups. This guide was initially developed prior to the commencement of PASSPORT, but was modified during the study, informed by the analysis of the recorded patient interviews and the completed data collection forms (see Appendix 10)

5.3.3 Data analysis

I. Data collection forms from the patient interviews were analysed manually to identify commonalities and differences in how individual questions were answered by healthcare professionals, and to examine free text entries. These data were supplemented by analysing the audio or video recordings of stratification interviews where available, closely examining the interactions between patients and healthcare professionals and looking for patterns or themes in how different healthcare professionals performed the risk stratification. All transcripts (or video) recordings of risk stratification interviews were read (or watched) 2-3 times during the analysis, in a process of constant comparison. I recorded my observations and reflections on these interviews using field notes, and these findings informed modifications to the topic guide used for the subsequent healthcare worker interviews and focus groups. For example, when it became clear that non-allergists were uncertain about how to categorise and interpret 'rash' histories, additional questions exploring this were added, such as how (all) healthcare professionals felt this problem could be addressed.

II. After reading and re-read the initial 3-4 transcripts from the healthcare professional interviews and focus groups conducted at the end of the study, I undertook line by line coding and developed a codebook. I shared this codebook with Dr Rousseau, the qualitative supervisor for this work, who had independently read the transcripts and made field notes. Once the codebook was agreed, I applied this to the remaining dataset, adding to and amending the codebook as new ideas were generated from the data. This approach facilitated a rich understanding of the data, allowing me to develop themes which are detailed in the sections below. A focused, descriptive approach was taken throughout the analysis, triangulating observations from all sources and using an iterative process of theme development. NVivo software (version 14.0) was used for ease of data handling.

5.4 Results

5.4.1 Patient interviews

A total of 202 completed data collection forms were available for analysis from 101 patients. A total of 27 of these patient interviews were audio/video recorded. Among these, seven patients had both the allergist and non-allergist interviews recorded, eight had just the non-allergist interview recorded, and five had just the allergist interview. For the remaining patient interviews which were not recorded, this was typically because the healthcare professional did not have a device available to record the interview over the phone and the patient preferred not to be interviewed on a virtual platform (or lacked the digital capacity for this) which would have facilitated a recording.

5.4.2 Healthcare professional interviews and focus groups

Seven healthcare professionals (referred to for the remainder of this chapter as 'users', for ease) were interviewed at the end of the study. They included three allergists (consultant allergists or immunologists) and four non-allergists (comprising consultant anaesthetists and pre-operative nurses). One allergist was interviewed alone, the other two together by choice and for convenience. Four non-allergists were interviewed in groups of two. The concepts and themes which emerged during analysis of these data mapped to three key domains:

1. Usability and user experience

2. The role of training and support

3. Optimisation strategies for future use of the tool.

5.4.3 Usability and user experience

5.4.3.1 Structure and layout of the tool

All users commented that simply asking each question within the tool in turn, felt awkward and non-intuitive. They found it more intuitive to start with an open-ended question, inviting patients to simply describe what happened when they took penicillin.

NON-ALLERGIST 1*: Most of these patients, they want to just tell you their story….. you just let them speak and they basically tell you pretty much most of what you want to know*

ALLERGIST 1: I have my own way of taking the history from the patients.

NON-ALLERGIST 1: It doesn't always seem like it flowed with the conversation [I] was having with the patient

NON-ALLERGIST 2*: from my perspective, I feel like…in a way that it would be easier for me to ask the history of the event first, and [then] dissect all the symptoms*

Non-allergists noted repetition when asking with questions in strict order, particularly when asking the questions about rashes. By contrast, analysis of the interviews recorded with allergists revealed that they generally obtained all the relevant information about a particular symptom (e.g. rash) in one step.

NON-ALLERGIST 3: [*the patient said "I got a rash"] But then when you look, yes, we cover rash in part A and then you reach the Part B, there's rash [again], but rash and blistering and….they couldn't remember if they had blistering….. it was a bit confusing for me sometimes*

5.4.3.2 Making a risk stratification decision

Overall, the tool was viewed by non-allergists as an 'aide-memoire' for taking an allergy history and ensuring high risk symptoms were not missed, rather than replacing the process of history-taking. They described needing to *interpret* patient symptoms, rather than simply recording the patient's answers to questions. This was because patients generally reported

symptoms in a way which did not fit neatly with available options for answers within the tool. It was observed that anaesthetists were generally more confident determining if the patient had comorbidities which would preclude challenge testing.

NON-ALLERGIST 3: I just made it open and then let the patient, you know, talk about the experience. And then I like went through the list of signs and symptoms just to check to see if they missed anything when they were describing their experience.

This interpretative process interacted with baseline knowledge and attitudes towards risk. For non-allergists, there was concern about the potential for exposing a genuinely allergic patient to penicillin, which translated into precautionary over-estimation of risk. This was particularly the case for anaesthetists, who described previous experience of witnessing severe allergic reactions in the perioperative setting. There was a perception that if a mistake were made which resulted in a bad outcome for the patient, this might result in medicolegal repercussions.

NON-ALLERGIST 2: ***Our experience [is that] basically we are injecting something, so our fear of being wrong is more triggered, I think.***

NON-ALLERGIST 1: ….***who's going to join me in court?***

Allergists and non-allergists both commented that the extremes of risk (very low or very high) were relatively easy to determine, but that there were ‘grey areas’ of uncertainty, where symptoms could be difficult to categorise. Such ‘grey areas’ represented the majority of the histories reported by patients.

ALLERGIST 3: ***I think in terms of identifying the low risk and high risk, I think it was fairly straightforward***

NON-ALLERGIST 4: The ones at both ends of the spectrum are really quite easy.

NON-ALLERGIST 2: [describing patients with unclear histories] what do we do? What is safe? You know, in some of the cases we probably can actually do it [give a test dose], but we are probably afraid of the risk…. so we go for the safest [option] and just don't do it, basically

Allergists commented that the tool provided an appropriately risk-averse approach, but noted there is always a possibility of severe allergy reactions on re-exposure to penicillin, even in low-risk patients.

5.4.3.3 Rash was the most common source of error

'Rash' was particularly difficult for non-allergists to categorise. We observed low confidence when determining the nature of the rash, occasional misunderstanding of 'red flag' features, and difficulty ascribing a rash to one of only two options in the tool (high risk or low risk).

NON-ALLERGIST 4: ***I found the rash thing the hardest, because I think we're only given sort of two options***

NON-ALLERGIST 2: [describing some of the rash histories]…. so they didn't fit in any of the boxes

NON-ALLERGIST 4: ..you had very strict criteria and sometimes my rashes didn't fit in either of them…..So I then can't make a decision about whether this is high risk or medium risk.

Patients often had poor recall the timing of the rash in relation to the first dose of penicillin. Non-allergists typically resolved this uncertainty by simply categorising the patient as ‘unsuitable’/’unknown’.

NON-ALLERGIST 4: ***the vast majority of my patients, the reaction was 25 years ago and they just can't remember the timeline…..*****so** ***I'll probably just put, ‘I don't know’ [‘uncertain’ risk outcome].***

NON-ALLERGIST 3: it's more the patient. I can't give a more accurate or properly detailed answer, to decide how we should categorise them

Interview recordings highlighted that allergists were able to pick out the key features of the rash more succinctly than non-allergists and were more confident in identifying red flags. Nevertheless, they commented that rash can be a challenging symptom for any users, and described specific examples which could lead to confusion.

ALLERGIST 1: ***…from [my] clinical practise many patients call hives ‘blisters’, which is confusing…..actually trying to tease out what they mean by blister is not always that straightforward.***

ALLERGIST 2: how do you define a low risk rash without specifying too much, [whilst] making sure that a high-risk rash is not missed?… it's very tricky.

Interview recordings for one of the patients demonstrates some of the different interpretation of rash symptoms between allergists and non-allergists:

1. **NON-ALLERGIST: And how was that rash? Was it raised? Did the skin feel hot?**

PATIENT X: It was bright red and quite bumpy and raised, it didn't peel off, and extremely itchy.

2. **ALLERGIST: What sort of rash? Was it itchy? Blistering?**

PATIENT X: It was itchy and raised and very, very red from what I can remember.

So it was raised, itchy, and how long did it take to resolve?

PATIENT X: Oh God. I want to say a few days but I don't know.

The non-allergist determined that this rash was non-urticarial, whilst the allergist deemed it to be urticarial.

There was mixed understanding about the significance of uneventful re-exposure to a culprit penicillin. Although the tool assigns this as a low-risk symptom, this was inconsistently followed, especially if the index reaction was reported to be very severe.

NON-ALLERGIST 1: ***I probably would have said unsuitable [high risk] if the previous reaction was anaphylaxis***

NON-ALLERGIST 4: If somebody's had a second course of antibiotics completely symptom free, I would say that they are not allergic. That would be an absolute 10 out of 10 rubber stamp OK.

5.4.4 The role of training and support

5.4.4.1 Allergy training

All non-allergists described a need for allergy training to increase their confidence in using the tool. There was a widespread perception that knowledge and experience are required for the interpretation of symptoms, and that the process of history-taking cannot be reduced to a checklist.

NON-ALLERGIST 4: ***You can't just get the greengrocer to ask the questions, because they won't understand the answers…..it doesn't matter how good you make your tool, there will always be scribblings around it.***

Users varied in their perceptions of what form training should take. Some thought simple didactic tutorials would be sufficient, whilst others commented that experiential training through working with allergy specialists in clinic would be helpful.

NON-ALLERGIST 3: ***you can't get capture everything from a lecture.. it would be good to actually be in the clinic and see how the allergist just manoeuvres around the conversations with the patient to get an accurate history.***

NON-ALLERGIST 4: ***..if I [had an] education session on allergic reactions….my understanding of allergies would be better and then I would be better able to sort of ask around any of the questions.***

NON-ALLERGIST 2: ***Education is always welcome and probably makes us feel more secure in our decisions as well.***

Allergists commented that this training was an ongoing requirement, rather than one-off need. This was mostly based on their own experience of training and supporting non-allergists in research or clinical settings in their own hospital.

ALLERGIST 1: ***I think institutional memory is important….training and refreshing the training of people involved in the pathway would be essential, because there's a relatively high turnover of personnel***

ALLERGIST 1: in our unit we have a competency based assessment for nurses and physicians who want to do penicillin delabelling…..that could be standardised across various places

5.4.4.2 Support from allergy specialists

All healthcare professionals perceived a need for specialist allergy input, to increase accuracy and safety. This was particularly important for the 'grey area' patients described above. Phone advice was generally considered adequate.

NON-ALLERGIST 4: I think, you know, so that you don't have an absolute hoo-ha on your hands it would be sensible for more than one person to look at those **[patients with unclear histories]**

NON-ALLERGIST 4: ***anyone where I kind of thought, oh, actually I feel a little bit [unsure] about this, I would then want to run that past an immunologist***

NON-ALLERGIST 1: ***I think having someone as that, I don't know, lead or point of reference makes it easier.***

Allergists described their experience of providing such support in routine clinical practice.

ALLERGIST 1: ..this works best in my experience, if there is a helpful specialist at the end of the line where people can sometimes enquire when they're not sure, rather than being in a complete isolation and just doing it on their own. I think for the for the most part, they can do it independently, but [they need] to have the reassurance [of] being able to pick up a phone and speak to somebody.

ALLERGIST 2: ***I really think to make it sustainable, it needs to be linked to an allergy service***

ALLERGIST 2: one thing we've tried here for example, is to make it nurse led and that's becoming very challenging because they really need the input of someone [with specialist expertise]

5.4.5 Optimisation strategies for future use of the tool

5.4.5.1 Standardisation of risk thresholds

Our data revealed differences in risk stratification between the allergists themselves. This undermines to some degree the use of allergist assessments as the 'gold standard' against which non-allergists assessments were based in PASSPORT. For example, patients with no recollection of their allergy reaction were deemed low-risk by some allergists, but high-risk by others. This specific scenario accounted for some of the high-risk misclassifications by non-allergists. These differences appear to reflect variation in real-world allergy practice, a problem acknowledged and debated by allergists during focus groups.

ALLERGIST 1: ***I think there's a disagreement between the specialists as well, for example, patients who can't give you any history and it's a childhood reaction. You know, some***

people might be comfortable to just go for a direct challenge test [but] some people might want to bring them in for skin testing [first].

ALLERGIST 3: ***it's also very centre specific. We're in [a different centre] and we have a one-stop shop, we even do the patch test for drugs. So I might have been a bit more reluctant to go straight to challenge if I know that I don't have to. It's just a question of the sort of the experience you've had.***

5.4.5.2 Minor amendments to the tool may improve accuracy and usability

Most of the suggested changes focussed on the history of rash. Allergists commented that pictures of different rashes might help patients, and increase non-allergist confidence in rash assessment. All users felt that additional questions around rash would be useful.

NON-ALLERGIST 4: ***you need a series of tick boxes. Was it a red rash, a flat rash, an urticarial rash, a blistering rash? And then you can decide afterwards whether it's important or not. I think trying to split it [the rash history] from the start into 'important' and 'not important' kind of misses out a lot of the rashes in between.***

It was perceived that having more questions might improve accuracy of the tool, but at the expense of overall useability. No users perceived benefit in removing questions.

ALLERGIST 2: ***I think it's as simple as it can get really.***

ALLERGIST 3: So basically, if you maybe define the benign rashes better, that's the only thing you'd actually need to do .

NON-ALLERGIST 4: ***…if you gave me [just] 4 or 5 questions to ask and you wanted to give them [a test dose of] penicillin after that, I'd have to probably say 'no' because I've not got enough information.***

5.5 Discussion

This evaluation explored the real-world performance of a risk stratification tool used by non-allergists, in an undifferentiated population of adult surgical patients, without any support from allergy specialists. The key finding was that non-allergists lack confidence in risk stratification, particularly when patient recall is limited, resulting in the precautionary overestimation of risk. At the same time, fundamental misunderstandings about allergy resulted in potentially harmful underestimation of risk. The tool appears to function as an 'aide-memoire', rather than a comprehensive checklist to cover all possible patient responses, because patients often report signs or symptoms which do not fit neatly into the options available in the tool. Minor modifications to the tool, especially to questions about 'rash', might improve its usability and accuracy. However, users still need to be able to interpret and contextualise symptoms, and the tool was not perceived by users to be a replacement for clinical acumen and experience. All healthcare participants described a need for training of non-allergists to increase confidence, as well as access to allergy specialists for advice.

Previous research has examined the safety and efficacy of delabelling pathways delivered by a variety of non-allergist healthcare professionals. A recent systematic review and meta-analysis included 69 of these studies (5019 patients) and concluded that this both safe and efficacious (121). However, the patient populations included were highly heterogenous and publication bias was found to be high. Many studies examined the performance of risk stratification tools in a pre-selected cohort of patients found to be low-risk following allergy testing by specialists, or included substantial input from allergy specialists (120, 179, 195).

This limits our understanding of how non-allergists might perform risk stratification in real-world practice, without support from allergists.

Qualitative work exploring the non-allergist perspective on delabelling in the UK and US, found that non-allergists perceive this as an important aspect of patient care, but are uncertain about how to elicit and interpret an allergy history (188, 207). Unsurprisingly, this was particularly the case when patients had limited recall of their history. There was a perceived requirement for allergy training and ongoing specialist support, and non-allergists worried about precipitating an allergic reaction during delabelling. These findings are supported by a multicentre study of non-allergist delabelling in 2024 which I co-led (the SPACE study, detailed in Chapter 3), in which the non-allergists (nurses, pharmacists, anaesthetists and physicians) described the risk stratification process as being more complex than anticipated. It was noted that training requirements for non-allergists varied depending on baseline knowledge and experience (180). Safety and personal liability were key concerns among non-allergists, with support from allergy specialists viewed as essential for developing a sustainable delabelling pathway. Previous qualitative research among general practitioners in the UK highlighted similar concerns about making risk-based judgements about the allergy history without the benefit of specialist support (127).

5.5.1 Strengths and weaknesses

The key strength of this process evaluation is that it provides a real-world, unbiased understanding of non-allergist performance when using the risk stratification tool. At the time of writing, this is the most robust assessment of the use of such a tool, offering novel and revealing insights into the experience and perspectives of non-allergists. Important barriers to the use of the tool are identified, and commonalities and differences in approach between non-allergists and allergists are clearly highlighted. The findings define important knowledge gaps and areas of reduced confidence among non-allergists, and will help determine how the tool could be modified to improve accuracy and usability.

The main limitations are around generalisability ('transferability') of the data. Despite diversity in terms of sex and age, few patients of ethnic background were recruited. Further, our results may not reflect the experience and perspectives of non-surgical patient cohorts, for whom the drivers and potential benefits of delabelling may differ substantially. Even within the cohort examined, there may be important aspects of the patient-healthcare professional interaction which have been missed because not all interviews could be recorded due for logistical or other reasons. Lastly, with only three participating allergists, the wider views of the allergy community may not be well represented in this research.

5.6 Summary

The PASSPORT process evaluation provides detailed understanding of how non-allergists use the risk stratification tool and the challenges they experience. Non-allergists lack confidence when eliciting an allergy history, and usually resolve this uncertainty by taking an excessively cautious approach to risk stratification. In parallel, important knowledge gaps can lead to potentially harmful underestimation of risk. Particular challenges described by non-allergists include determining risk level when the patient has poor recall of their history, and the difficulty of categorising patient histories which do not easily fit the available options within the tool. Minor modifications, particularly around 'rash' questions, may improve usability. There is a substantial need for allergy training among non-allergists, as well as for ongoing support and input from allergy specialists. These factors will need to be comprehensively addressed to facilitate successful implementation of the tool into routine delabelling pathways. Future research will need to include greater diversity of both patients and healthcare professionals, to understand whether the results presented here are generalisable to other settings.

6 Understanding patients' perceptions, knowledge and experience of perioperative allergic reactions: a qualitative interview study

6.1 Background and rationale

Allergic reactions to drugs are a life-threatening complication which can occur in any patient undergoing surgery and anaesthesia. Estimates suggest an incidence of between 1:2000 – 1:10,000, with survivors experiencing both immediate and long-term harm (7, 129). To prevent further allergic reactions occurring in the future, the responsible drug must be identified through allergy testing and then carefully avoided (6, 57).

The culprit drug is typically one used only in the perioperative setting, such as a neuromuscular blocking agent (NMBA), but may be a more widely used drug such as an antibiotic. Despite the severity and long-term impact of perioperative allergy, very little is known about the patient perspective on these reactions and the lived experience of them. To date, the only work examining the psychological impact of perioperative allergy is the 6th National Audit Project of the Royal College of Anaesthetists in 2019 (7). Several patients in this study reported psychological harm following the suspected reaction, including features consistent with post-traumatic stress disorder.

In addition, there are few data to help us understand patient behaviour around managing their allergy diagnosis and reducing the risk of further reactions. My clinical experience in the perioperative allergy clinic is that it can be difficult for patients to make sense of their diagnosis and its implications, but we have limited understanding of how this might affect patient behaviour during future healthcare encounters, or on their daily lives.

Qualitative research in patients living with allergy in the non-perioperative setting has found that patients experience frustration, anxiety, and a sense of isolation. Many patients display avoidant behaviour in order to reduce perceived risk from further allergic reactions (168, 208-213). However, this research is predominantly focussed on children with food allergies, or adults experiencing adverse drug reactions in the non-perioperative setting. Whilst providing some insights into the patient experience of allergy, these data may not be generalisable to the unique setting of perioperative reactions.

6.2 Aims and objectives

6.2.1 Aims

My overarching aim was to gain deeper understanding of the patient perspective from initial event to eventual diagnosis, and insights into how this journey might be improved to mitigate both the psychological harm from these events and the risk of future reactions. I sought to understand patient perceptions and knowledge about the reaction itself, and to identify what impact this had on the patients' daily lives. I also aimed to explore expectations around allergy testing, perceptions about its safety and accuracy, understanding of the eventual allergy diagnosis, and perceptions and behaviours around future healthcare interactions.

6.2.2 Objectives

To address these aims, I set the following objectives:

- To develop themes which describe the range of patient perspectives, behaviours and attitudes in relation to their suspected perioperative allergic event, the allergy testing at clinic, and their eventual diagnosis
- To explore the potential impact of the allergy diagnosis on the patients' future healthcare interactions
- To determine how the care pathway might be improved for patients

6.3 Methods

6.3.1 Study design, inclusion and exclusion criteria

This was a qualitative study of patients who had experienced suspected perioperative allergic reactions and been referred to the Leeds Regional Anaesthetic Allergy Clinic in Leeds Teaching Hospitals NHS Trust. Research Ethics Committee approval as obtained in March 2023 (REC reference 23/NE/0058, HRA approval April 2023. See Appendix 8.11.4 for approvals letter). Leeds Teaching Hospitals NHS Trust agreed to sponsor the study (sponsor number GS23/156788). All patients scheduled to attend the Yorkshire Perioperative Allergy Clinic were considered eligible for inclusion. Exclusion criteria included patients who had

insufficient time to be sent a patient information leaflet due to the clinical urgency of the clinic appointment, and patients who were unwilling or unable to consent.

6.3.2 Study setting

The Yorkshire Perioperative Allergy Clinic receives adult patient referrals from NHS and private hospitals covering a population of around 2.5 million people. More than 650 patients have been referred for investigation in the past 15 years. The clinic comprises a multiprofessional team with anaesthetic, immunology and specialist nursing input. A clinic is held once per month, typically with four patients scheduled to attend each clinic.

6.3.3 Screening, recruitment and consent processes

Clinic lists were screened by me, with a patient information leaflet sent to all potentially eligible patients 2-4 weeks prior to their scheduled appointment. I then contacted patients by telephone 1 – 2 weeks later, using a purposive approach to sampling from each clinic in which I aimed for maximum diversity in terms of age, sex and ethnicity. Patients who agreed to participate provided formal written consent to undertake two audio-recorded interviews, and for anonymised extracts from these interviews to be used in future publications.

6.3.4 Data collection

Patients were interviewed by me approximately one week before and one week after their clinic appointments. These were semi-structured interviews lasting approximately 25-45 minutes. I did not attend clinics in which participating patients were included and ensured, as far as possible, that the other healthcare professionals in clinic were unaware of which patients had been recruited in any particular clinic. All interviews were conducted by me and recorded using a handheld device.

During the interviews, I used a topic guide which I had developed during my fellowship application process (Appendix 10). This guide was informed by my clinical experience in the perioperative allergy clinic, the experience of others in the clinic, and through consultation

with patients and members of the public which I undertook in the early stages of my fellowship application. This consultation process included patients with lived experience of perioperative allergy who had previously attended clinic for investigation, as well as members of the public who formed a local patient advisory group, providing input on various aspects of my fellowship. The guide provided prompts to ensure specific questions were covered, but also included open ended questions to encourage participants to talk freely about their experiences. At the beginning of the interviews, I explained to patients that I was a researcher for the perioperative allergy clinic and I remained in this researcher role when they had questions about the clinic. However, if a patient was clearly very anxious about the clinic, I 'stepped out' of my researcher role and offered to discuss these concerns at the end of the interview. Recordings were transcribed verbatim using a secure, commercial transcription service (Hightail transcription services).

6.3.5 Data analysis

Data were analysed using a codebook thematic analysis approach, in which codes were developed and refined iteratively, then applied to each subsequent transcript. The decision to use this approach was made at the design stage of my fellowship, following discussion with the qualitative supervisor for my PhD (Dr Rousseau). This approach is particularly suited to analysis by more than one researcher, since codes can be shared, discussed and revised in an iterative process throughout the analysis, ensuring consistency and reliability (214). This approach also reflected the lack of prior research in this area and the need for an entirely open, inductive process which would allow themes to emerge from the data (209). In that respect, it resembles the use of grounded theory, in which theory develops from the data rather than having a theoretical preconception about the data.

The initial three transcripts were read and coded independently by me, and then by Dr Rousseau. We met to discuss my initial coding ideas and agree a codebook. After this, transcripts were read, re-read and coded by me as each set of interviews was completed. Using a process of constant comparison throughout the study, I was able to continually refine and develop the codebook, and overarching themes and sub themes were developed iteratively from this. I met with Dr Rousseau regularly throughout the study to discuss the

analysis and emerging themes. I used NVivo software (version 14.23.2) for ease of data handling, having undertaken online training on this. Patients were anonymised in the manuscript using pseudonyms, with no specific details of age, surgery, exact diagnosis or other identifiable information. Participant sex was retained, as this was pertinent to some of the identified themes. I used the COREQ checklist to guide reporting of the study.

6.4 Results

Data collection took place between September 2023 and May 2024. Thematic saturation appeared to have occurred after eight patients were interviewed. Recruitment continued for a further three patients to ensure no new themes could be identified, at which point recruitment ceased. In total, 22 interviews were completed, in 11 patients. Three patients were male; all were white British. Patient ages ranged from 39 to 88 years. Following investigation, six patients were given a confirmed diagnosis of perioperative allergy and advised to avoid either single or multiple drugs. A further three patients were deemed to have suffered a severe perioperative adverse reaction of unclear cause and were advised to avoid multiple drugs as a precaution. Two patients were confirmed not to have suffered perioperative anaphylaxis and were given an alternative diagnosis; no avoidance advice was given for these patients.

Four overarching themes were developed during analysis: (1) the impact of being unconscious ('absent') during the reaction; (2) the implications of perioperative allergy for the patient; (3) understanding of allergy and allergy testing; and (4) perception of risk and vulnerability during surgery. See Table 24 and Figure 23. These are discussed below, alongside illustrative quotations.

Table 24: Themes, sub-themes and key messages for healthcare professionals

Main themes	Sub-themes	Key messages for health professionals
Impact of being unconscious ('absent') during the reaction	• Being unconscious during the reaction may be protective for some patients • Patients may struggle to understand the significance and implications of the reaction, because they are unconscious when it happens • Patients often remain uncertain about what happened	➢ Perioperative allergic reactions are a source of substantial and persistent anxiety, which can impact daily life ➢ The negative psychological impact may be mitigated by detailed explanations, provided once the patient is fully awake and able to retain information ➢ Written information should also be provided. This must detail which drugs should be avoided pending allergy testing. ➢ Patients have limited experience of allergy testing and may perceive this as risky or dangerous. Clear information about testing may reduce anxiety. ➢ Patients may assume their allergy diagnosis is automatically accessible to future anaesthetists. Vigilance is required to ensure that a previous allergy diagnosis is picked up and acted on. ➢ Patients may misunderstand or have poor recall of their allergy diagnosis, particularly when multiple drugs must be avoided, and when drug names are unfamiliar (eg NMBAs).
Meaning and implications of perioperative allergy for the patient	• Concern about the reaction can impact day-to-day life • Patients can find it difficult to accept they may have become allergic to a perioperative drug • The perioperative reaction interacts with other major life issues	
Understanding of allergy and allergy testing	• The importance of pre-clinic information • Difficulty understanding and remembering the diagnosis.	
Perception of risk and vulnerability	• Trust in healthcare professionals and systems	

during surgery and anaesthesia	• Responsibility for safety during future surgery • Willingness to undergo further surgery	Always check the clinic outcome before proceeding with anaesthesia. ➢ Patients are likely to be extremely anxious about future anaesthesia and may need additional counselling and support in the perioperative period.

6.4.1 Impact of being unconscious ('absent') during the reaction

Patients are typically (although not universally) unconscious at the time of the suspected allergic reaction. This creates a key contextual difference between perioperative and other types of allergy (for example food allergy) where there is a clearly remembered sequence of events and good recall of the physical symptoms experienced. In perioperative allergy, patients typically discover that they have suffered a suspected reaction only after they have regained consciousness, at which point the allergic symptoms are largely resolved. At this point, it is unconfirmed whether the event was due to allergy or a non-allergic problem, since this can only be determined through investigation at an allergy clinic. Collectively, these factors result in a unique patient experience which profoundly impacts the emotional and cognitive response to the event.

6.4.1.1 Being unconscious during the reaction may be protective for some patients

One patient, in whom the reaction occurred before the onset of unconsciousness, had distressing recall of the event.

Arthur: …..It were like a big bang and straight away, I had to shout out, "I'm being strangled." It felt as though there were a rope round me neck and people were pulling me backwards **(Pre-clinic interview)**

However, all other patients were unconscious at the time of the event, and several described relief at being unaware of the reaction as it happened.

Susan: ***….I'm taking positives that I was completely unaware because it must be incredibly frightening to be aware it's happening*****. (Pre-clinic interview)**

Gordon: [asked if upset when woken up and told what had happened] Not really, because I was, to me it was all over already, it's just part of getting better… **(Pre-clinic interview)**

A subset of patients reported low levels of anxiety about the event whilst at the same time reporting behaviours seemingly at odds with this. For example, Arthur denied being worried about what happened, yet refused to undergo surgery during a subsequent hospital admission (prior to his clinic visit), due to concerns about anaesthetic safety.

6.4.1.2 Patients may struggle to understand the significance and implications of the reaction, because they are unconscious when it happens

Several patients recalled feeling confused and uncertain in the recovery period. In part, this might be attributable to the effects of the recent general anaesthetic, which can limit the absorption and retention of information. There was also dissonance for some patients between how they felt, and how unwell they were told they had been whilst asleep. This appeared to make it harder to process the event. The words used by healthcare professionals to describe the reaction were often recalled as alarming or frightening.

Amanda: [I was….]… very, very tired and really struggling to take in what they were saying to me. I just wanted to go back to sleep and it was only really the following day that my, when my husband was talking to me that I really was kind of taking it all onboard. I just didn't really want to know about it (Pre-clinic interview).

Susan: I woke up and apart from lots of extra tubes and people monitoring me, I felt no sort of particularly different to when I went in. In fact, I felt almost a bit of a fraud to be in ICU with all these incredibly poorly people…, and there's me just like, well I don't really know what went on, and I didn't see it sort of thing. (Pre-clinic interview).

Being unconscious during the reaction appeared to make it easier for some patients to dismiss or minimise the importance of the event. This was particularly the case when surgery was important or time-critical.

Gillian: ***I obviously didn't realise the seriousness of it, and initially when I was first discharged I was just more disappointed to not have the operation, and I didn't actually realise the seriousness of it because nobody had explained it.*** **(Pre-clinic interview)**

Marian: I mean, I thought well I'm alive, I've come out of it, so it can't have been serious...

Once patients were more awake and able to understand what had happened, this knowledge was often very distressing.

Susan: I think it was in the middle of the night, when I thought, oh,……that meant for a very small moment of time I died, as it were. And so I had a little bit of a weep then I think, that, I think that's when it sort of dawned on me, the severity of what had happened……these things happen in the middle of the night don't they, and in the dark and the quiet. (Pre-clinic interview)

6.4.1.3 Patients often remain uncertain about what happened

Some patients recalled having detailed conversations about the event with healthcare professionals and valued these interactions, but most patients had no recall of such discussions, or being provided with written information, and their uncertainty about what happened extended into the post-discharge period. For many, the nature and severity of the reaction therefore only became clear much later, for example during surgical follow-up or even at the allergy clinic itself, and was a shock.

Jane …..[recalling talking to the surgeon several weeks later] ***he just said "you gave me a really nasty shock, you know, and your blood pressure just totally", his words were …"you frightened us all". And so I thought "ooh blimey if I frightened you then maybe should be slightly more aware of what happened to me.*** **(Pre-clinic interview)**

Gillian:…… it wasn't until I'd spoken to..the colorectal surgeon a couple of weeks ago that he kind of gave me the full extent of what had happened…..

Arthur: ….. I've always been in industry and if anything went wrong, used to be people used to get wrong and try to find out why it wrong. But nobody said anything to me how I left out, completely, I didn't like that

For one patient, who was not provided with information about drugs to avoid whilst waiting for investigation, there was a genuine risk of re-exposure to the culprit drug since this was an antibiotic she took frequently and had a supply of at home. Once this risk was appreciated by the patient, she was distressed by the lack of information given before discharge.

6.4.2 Meaning and implications of perioperative allergy for the patient

6.4.2.1 Concern about the reaction can impact day-to-day life

For many, there was a substantial negative impact from the perioperative event on their daily lives in the weeks or months whilst they waited for allergy testing. Several described a strong sense of needing to protect themselves from the risk of accidents which might lead to needing further surgery and anaesthesia.

Amanda: I'd quite frankly like to wrap myself up in cotton wool and sit here until I get myself sorted out….because there's more chance of me hurting myself if I'm out and about…… I won't go on an electric bike, I won't do anything at the moment. It has rocked my confidence I suppose……I'm quite happy almost living in my little bubble at the moment, if I can avoid things I do it. **(Pre-clinic interview).**

Dorothy: ….I'm trying to be careful so I don't, so I don't fall again or anything like that.**(Pre-clinic interview)**

Jane: …..I think that's why I'm a bit more careful when I'm walking about and stuT, because I'm so frightened of falling, and summit happen to what I've had done to me legs, and having to go back in and have more surgery.**(Pre-clinic interview)**

Brian: Oh, it's definitely changing how I live….. I mean I ride a motorbike, I'm just more cautious ….I do street lighting…so I have to go up in the, up in one of the hoists and I'm just a bit if somebody ran into me, I wear a harness but that still doesn't stop you getting tipped out the bucket and getting injured….**(Pre-clinic interview)**

For one patient, who worked in a healthcare environment, there was anxiety around potentially harmful re-exposure to drugs or chemicals.

Gillian …I'm actually really worried about going back [to work] because, yes, I'm around chemicals, I'm around drugs, so yes it's sort of….well not avoiding going out, but being careful of where I go….(Pre-clinic interview)

Several patients described persistent anxiety, flashbacks or intrusive thoughts about the event, often associated with a sense of increased vulnerability about future anaesthesia.

Amanda: you had an awful lot of time to think about that and as I said it made you feel quite vulnerable and anxious….
[in relation to needing further surgery]… I would do things differently. I maybe would write a letter and daft things like that you see in the movies….**(Post-clinic interview)**

Gillian: [reporting what her husband said to her] ….something like, well what would he have done? You know if something had have, if it had, well, if it hadn't have been the right outcome, what would he have done? And that kind of, that traumatised me……**(Post-clinic interview)**

Dorothy: Well I keep going over it in my head and I wish I didn't so, no sometimes, and it might crop up in a conversation, somebody'll ask you a question and, and it all comes back to you. **(Pre-clinic interview)**

Susan: I'm thinking has my heart stopped, so does that, you know, from what you hear in the world, can that have a long-term effect, well you know, has it hurt my brain, or you know, that kind of thing **(Post-clinic interview)**

However, other patients reported more positive reflections.

Susan: I think it's another one of those little kick up the bottoms to say, you know, don't put things off….. just that little reminder that things could just have easily have changed another way, just make sure that you get out more, you do things that you want to do… **(Post-clinic interview)**

6.4.2.2 Patients can find it difficult to accept they may have become allergic to a drug used in the perioperative setting

Patients who had experienced multiple previous episodes of uneventful anaesthesia appeared to find it hard to accept they might have suffered an allergic reaction.

Marian ***….. I knew I wasn't allergic to anything because I've had that many operations, if you're going to be allergic to it you'd do it when you'd just started your operations wouldn't you, not nearly 30 operations down the line.*** **(Post-clinic interview)**

Rebecca: …..apparently I'd had a reaction to something, anaesthetic but they'd given me the same as what I've had before. **(Post-clinic interview).**

6.4.2.3 The perioperative reaction interacts with other major life issues

For several patients, the perioperative event and need for subsequent investigation simply represented an obstacle to receiving important surgical care.

Rebecca: I were so annoyed because I'd not had the surgery and in the meantime I've got these tumours still growing …..and I've got to wait to see what it is that I'm allergic to before they can do anything. (Pre-clinic interview)

Marian*: ….basically I think this is why I'm not getting me operation until they find out what's happened, do you know what I mean, so I'm sure they keep putting it off and putting it off…* **(Pre-clinic interview)**

Several patients had caring responsibilities for dependents. For some, this increased their frustration around perceived delays in testing, whilst for others it diminished the overall relevance and importance of testing.

Rebecca: [when asked if she would be worried about undergoing further surgery] ***It's not that I'm worried, it's I've got two kids..[*****with mental health issues*****]….so like it's getting them ready and prepared for me going in hospital and like it's just going to be them and their dad but then it's like messing them about because it's been done this... Because I've had, this will be me third operation…. so it's getting them ready and then if it gets cancelled then that's messed them about….*****(Pre-clinic interview)**

Arthur: [when asked whether he considers allergy testing to be useful for him]: Well, I just don't think that at my age, that anything can improve on what I've got already. I mean, I have a decent life, although I've got a wife who's got Alzheimer's. Most of the time I don't get anything for it but I take her anywhere she wants to go and I look after her, nurse her, cook for her, do the washing, do the ironing, I do most of the jobs in the house. (Pre-clinic interview).

6.4.3 Understanding of allergy and allergy testing

6.4.3.1 The importance of pre-clinic information

There was evidence of mixed understanding around both the process and importance of allergy testing. For some, there was sometimes a perception that testing was mainly for the benefit of future healthcare professionals, rather than the individual themselves.

Arthur [when asked if clinic will be useful for him] ***Not really for me, at my age, but if it's anything that can help people in the future…*****(Pre-clinic interview)**

Marian: ….I thought the amount of operations I've had it might be just one of them things, do you know what I mean, I didn't think it were a big deal really.

For others, testing was of paramount importance. This was particularly the case when surgery was time-critical.

Amanda: ….if a date was made available to me next week I'd cancel everything to go for it……

Some patients had a perception that communication between the referring hospital and the allergy clinic was poor, and that this contributed to a delay in accessing testing and further surgery. Whilst the study was not designed to identify the cause of any delays, it was possible to identify for some patients at least, that the perceived delay was simply the necessary wait required before testing could be undertaken (a minimum 4-6 week wait is recommended prior to skin testing, to reduce the risk of false negative results).

Rebecca:….. one of the big things that I think is quite wrong with NHS is communication and I think that's where there's like a big downfall in NHS. I feel bad saying that but there is. And it's like I'm in [referring hospital] and I'm getting treatment in [different hospital] and yet my doctors and hospital don't really communicate…… It's all on different networks intit? **(Pre-clinic interview).**

Gillian: Initially, because I had to chase the allergy appointment up and when I called, I called immunology and she just said it as a 27 week wait [laughs] I can't wait another 27

weeks, and then I ended up contacting somebody else and I had a bit of a meltdown. **(Post-clinic interview).**

Knowledge about allergy testing was often limited, with patients having little previous experience to draw on. Most patients expressed some anxiety about what would happen in the clinic, with concerns relating to suffering a further reaction when exposed to the culprit drug. Overall, however, there were high levels of trust that any risk would be appropriately managed by the healthcare professionals.

Susan: ……[I expect]…*they'll give me pin pricks, but I suppose although I know I'm in safe hands, there is that element of well you're going to test me for something that sent me completely doolally, you know……..I mean I'm not frightened, but you're just thinking, ooh, last time I came into contact with this it… it didn't have a good outcome….*(Pre-clinic interview)

Jane: So if I do have a bad reaction or summit, I know I'm in the right place, or I know I'll get looked after, but I really do need to know, you know. **(Pre-clinic interview)**

It became clear during interviews that pre-clinic information may have helped reduce anxiety. Most patients stated they would like written information, whereas others (particularly younger patients) would prefer videos. The amount of information patients felt was necessary, varied.

Dorothy: ***Well, I'd just like to know exactly what happens, whether, if they inject you again or, or put, I don't know, stick something on your arm or something like that*** **(Pre-clinic interview)**

Gillian: I suppose really just to expect sort of a step-by-step guide on what to expect

sort of when you get into clinic and what happens throughout the time that you're there. (Pre-clinic interview)

Kathryn: Just a little bit of detail. It doesn't have to be a lot. Just give you a general idea. (Pre-clinic interview)

6.4.3.2 Difficulty understanding and remembering the diagnosis.

Routinely available allergy tests are imperfect, and making a diagnosis with high certainty can be challenging. Patients may anticipate receiving a clear diagnosis of allergy to a single drug, but the reality is often less clear cut and avoidance of multiple drugs may be recommended. Patients appeared to have lower confidence in their diagnosis when multiple drug avoidance was recommended, or when skin testing results were ambiguous. For many patients, unfamiliar drug names were a further barrier to understanding and recall of their diagnosis (for example, neuromuscular blocking drugs). Several patients only had partial recall of their diagnosis, despite receiving both verbal and written confirmation. Inaccessible medical language in the clinic letter appeared to compound this difficulty. None of the patients who had been unsure about the diagnosis had considered asking their primary care doctor for further clarification.

Arthur: ***So all he said like was that the tests are clear and it were no, nothing to do with me.*** **(Post-clinic interview. Allergy confirmed to two drugs)**

Rebecca: ….because you forget stuff when you're in clinic and when you come out and then when you get the letter, it's all in medical terms, you're just like I don't have a clue what it's saying or what's what. **[Post-clinic interview - confirmed allergy to several related drugs]**

Kathryn: ***If I'd have had a positive answer saying "yes, you're definitely allergic to this", I think I would have felt a bit more positive than negative I think, yeah.*** **(Post-clinic interview. Negative skin tests to suspected culprit drug)**

Dorothy: Well I'm not really clear I just, I sort of, I just believe what they say and maybe send for the medal or whatever, this medallion you wear...[**Post-clinic interview, advised to avoid four drugs, unable to recall which*****]***

Conversely, where skin test results were clearly positive for one drug, patients generally had confidence in the diagnosis and better recall of this.

Amanda: ***….to be honest with you it was a total relief because they told me exactly what it was. There was no question as to what I was allergic to…*** **(Post-clinic interview. Allergy confirmed to a single drug)**

Brian: it's nice to know what's actually happened, having it worked out and it's a relief that now that I suppose it will go onto my record. **(Post-clinic interview)**

For some, the diagnosis appeared to provide closure on the event and allow the patient to move forward. However, for others, the allergy testing was unable to help them make sense of what had happened.

Susan: ***…..I was wanting more nitty-gritty, and in one sense it's completely irrelevant, because I slept through it, I came through it, and do you really need to know, but it's something that's happened to me, and I would like to know, you know, I would like to know.*** **(Post-clinic interview. Allergy confirmed to single drug, with avoidance of related drugs recommended).**

Dorothy: ….in a way it hasn't helped not much, I just, I'm still confused about it.

[When asked: 'did they explain to you what they thought might've been the problem?']

They did but sometimes I don't suppose everything stays in my head. **(Post-clinic interview)**

6.4.4 Perception of risk and vulnerability during surgery and anaesthesia

6.4.4.1 Trust in healthcare professionals and systems

Many patients expressed a sense of vulnerability during surgery and anaesthesia, which had existed before they suffered a suspected allergic reaction. Nevertheless, there were consistently high levels of trust in healthcare professionals, with only two patients (Marian and Arthur) describing a loss of trust following the perioperative reaction.

Marian: …..when you're under anaesthetic you don't know if you're close to death or not, do you know what I mean, so you're putting your life in their hands. **(Post-clinic interview)**

Rebecca: I just think because you've just got to have trust in people, haven't you and just it's their job at end of day, it's what they do and what they know…..**(Post-clinic interview)**

Brian: As long as they know [about the allergic reaction] I wouldn't be bothered, you put your life in their hands and I would willingly if I needed something done. **(Post-clinic interview)**

Amanda: [Is worrying about surgery new for you?] Absolutely. No, totally new. I would never question because I've had two major surgeries before and I've never had a problem…. I would never have thought it would have entered my head to be honest with you. **(Post-clinic interview)**

Marian: ***are they're doing their job properly……are they trying to rush things through and then they're making a mess of it to get next patient in…….. if it's not what I'm allergic to then I can only think it's summat they've done in theatre.*** **(Pre-clinic interview).**

For others, the event had caused them to be newly reflective on the potential risks of surgery and anaesthesia.

Susan***: But I would also guess that when I go into my operation,*** **[they will]** ***now obviously be aware of what's happened….. and I would like to think that they will be, you know, extra, they'll give me that extra bit of, you know, if I do need somebody to hold my hand, I'd like to think somebody would, you know?*** **(Post-clinic interview)**

6.4.4.2 Responsibility for safety during future surgery

There were mixed perceptions around whose responsibility it was to communicate the allergy diagnosis to future healthcare professionals. Several patients with confirmed allergy diagnoses considered it their responsibility, and planned to obtain a MedicAlert bracelet, tell their GP, and make sure family members were aware. One patient had concerns that despite taking these steps, there may still be issues with communicating the diagnosis, for example if travelling abroad.

Amanda: ***…you're just hoping that the right person's looking at the right thing, you're not in a foreign country and they can't read English, you know.*** **(Post-clinic interview)**

Kathryn: [Asked if will obtain MedicAlert]…Yes. I am going to do that. And I'm going to put it on me phone as well because I have a medical ID thing on me phone as well so…**(Post-clinic interview)**

However, many patients expressed ambivalence about their personal responsibility for communicating the allergy diagnosis to others. This usually related to an underlying assumption that the relevant information would be readily accessible to staff. Older patients generally perceived limited benefit from wearing a MedicAlert bracelet.

Jane: I think they'll just work out the best thing to do…they must know the sort of drugs that I had, that give me reactions, and so obviously they're not going to use the same sort of drugs are they?.....Because it'll be in me notes and that….. **(Post-clinic interview)**

Susan: [Asked if they think they will need to tell the next anaesthetist about the diagnosis] Well I would, I'd like to think the system would, well I know certainly the fact that I've had a suspected reaction to a specific drug, you know, when I've gone to my doctors, it was already on my system……. So I'm sure they will be aware of it……..everybody will ask the standard questions, are you allergic to anything. **(Post-clinic interview)**

Rebecca: [asked if planning to wear a MedicAlert] I don't know because it's like one of them things init, like I say where you don't come across it every day, so. But then again, if summat were to happen when I were out on street….**(Post-clinic interview)**

Dorothy: I might not bother, I don't know. I'm thinking about whether I should get it…[MedicAlert bracelet]. [Patient asked why]… It's maybe that and my age and everything else, you know. **(Post-clinic interview)**

6.4.4.3 Willingness to undergo further surgery

After receiving their allergy diagnosis, patients expressed a range of feelings about future surgery and anaesthesia. Several were still awaiting operations cancelled because of the suspected allergic reaction. In this group, one woman expressed the view that she felt safer

now that her allergy had been investigated and the healthcare team would be aware of this. However, the remaining patients expressed anxiety about their operation.

Rebecca: ***I've not allowed myself to think too much about it, otherwise they might not get me on that table.*** **(Post-clinic interview)**

For patients not awaiting surgery, there was near-universal anxiety about the prospect of needing this in the future, though interestingly, none stated they would actively avoid it.

Gordon: ***I think it would be in your mind but that's the gamble you've got to take intit, to get better.*** **(Post-clinic interview)**

Susan: I don't think I'll be confident enough to go, "Oh yes, I'll sail through this," you know, I think it will always be in the back of my mind. (Post-clinic interview)

Dorothy: If anything crops up that I need it, I would have to go through with it….(Post-clinic interview)

Kathryn: …..if I really needed then I'd have to go through it wouldn't I? (Post-clinic interview)

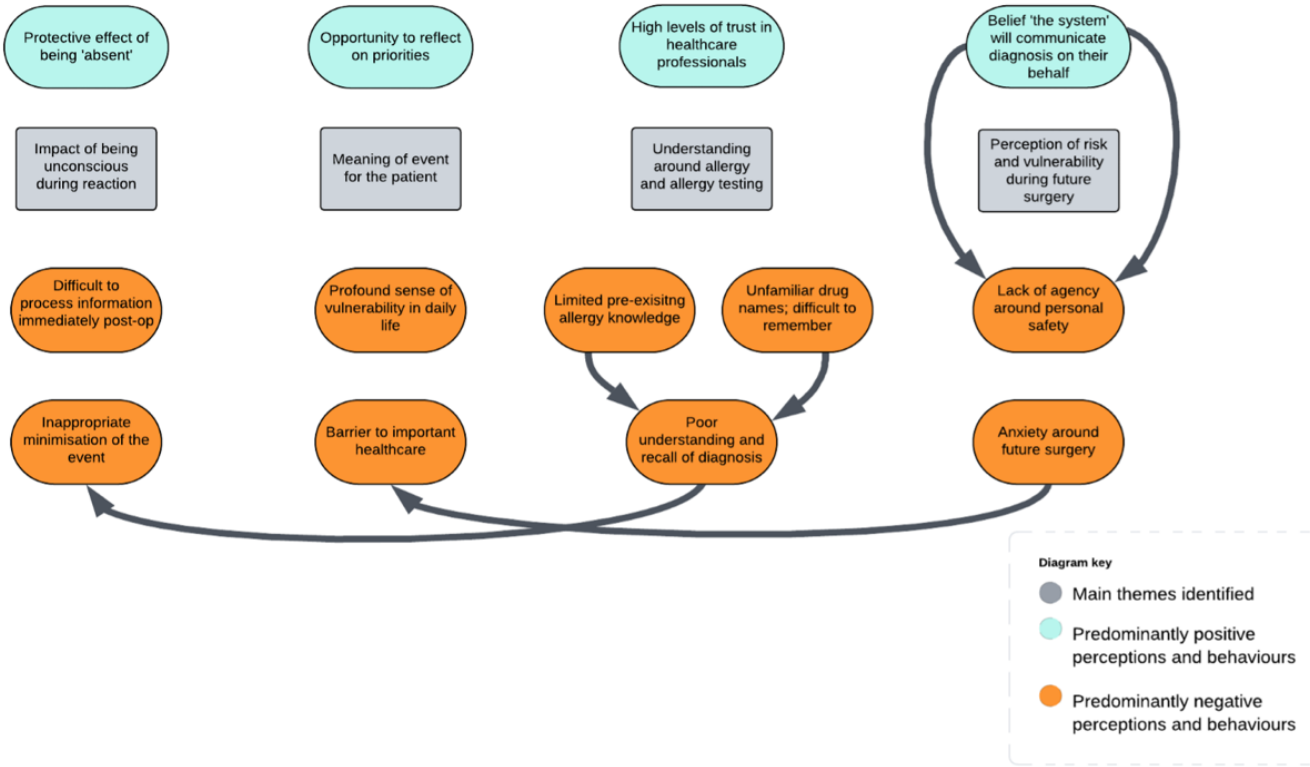


Figure 22: Patient perceptions, views and understanding about suspected perioperative allergic reactions: key themes and how these interact

6.5 Discussion

This is the first study that I am aware of to provide detailed understanding of the beliefs, behaviours and attitudes of patients who suffer suspected perioperative allergy. The key findings are that patients can experience substantial and persistent anxiety following such events, and there is an unmet need for information at each stage of the journey from event to diagnosis. Several patients demonstrated avoidant behaviour to reduce the risk of requiring further surgery, with some substantially limiting their daily activities to achieve this. The results also demonstrate that patients hold fundamental misunderstandings about their allergy diagnosis, and its implications for future healthcare. There was often poor, or inaccurate, recall of the diagnosis and the culprit drug(s) which must be avoided. A pervasive belief that 'the system' would communicate this information on their behalf appeared to lead

to a lack of agency around ensuring their own safety. This presents a clear risk for further allergic reactions from re-exposure to the culprit drug(s) during surgery or other healthcare interventions.

Previous research among patients living with allergic disorders has demonstrated high levels of anxiety, fear and frustration. Much of this work involves paediatric food allergy, where fear of exposure to a culprit food negatively impacts patients' perceived ability to live a normal life, creating a sense of isolation among both children and carers (208-213). High levels of anxiety have also been demonstrated among adult patients with suspected drug allergy; only one of these studies included perioperative allergy patients, and themes specific to the perioperative setting were not explored (168). A systematic review and meta-analysis of 45 observational studies examining health-related quality of life among patients with adverse drug reactions (including allergy), found significantly higher rates of depression and anxiety compared to healthy controls (215). Quality of life was particularly impacted when the drug caused severe reactions, including anaphylaxis. Studies using a validated drug allergy quality of life questionnaire have consistently found that the presence of more than one drug allergy label, and a severe index allergic reaction, are associated with worse quality of life (216-222). A large study in Turkey found that one quarter of patients had delayed medical treatment because of drug allergy concerns (223). In our cohort, pre-existing feelings of vulnerability during surgery and anaesthesia compounded the anxiety experienced following an allergic reaction. Being 'absent' during the reaction appeared to impact the subsequent emotional response, for some patients increasing a sense of vulnerability, whilst diminishing the perceived importance of the event for others. Most patients demonstrated heightened anxiety about future surgery, with some limiting daily activities to mitigate this risk.

The unmet need for better information at each stage of the journey was clear throughout. It can be challenging for healthcare professionals to communicate information effectively in the immediate aftermath of reactions because of the effects of the anaesthetic (224, 225). Nevertheless, only a minority of our cohort received written information explaining they had suffered a suspected allergic reaction, the names of the drugs they must avoid whilst waiting for allergy testing, or the next steps in terms of allergy clinic referral. There is national

guidance from the Royal College of Anaesthetists on the need to provide this information, with a template letter which can be downloaded for patients (137, 226-228). At least one patient was at significant risk of re-exposure to the culprit drug (an antibiotic) in the community whilst awaiting investigation, emphasising the critical importance of such information. Our data also suggest that patient information about allergy testing would be beneficial. The tests themselves were a source of anxiety and, in line with previous work, there were perceived shortfalls in accessing testing (229-231). Many of these concerns might be addressed with patient information resources detailing the process of allergy testing and providing reassurance about its safety. In contrast with other patient groups undergoing allergy testing, our cohort expressed no preference for the exact testing modality used (blood or skin tests) (230). However, we found that a proportion of patients still struggled to make sense of their diagnosis, or accurately recall the drugs they needed to avoid, particularly when drug names were unfamiliar. Previous work demonstrated that patients expressed reluctance to take a drug even when allergy to it had been excluded (232). Our work suggests that, in addition, patients may have lower confidence in the diagnosis when multiple drug allergies are diagnosed, or test results are ambiguous. The use of patient-centred information to specifically address these uncertainties may be helpful.

A key finding of concern was that patients often considered that responsibility for communicating their diagnosis lies with healthcare professionals, and that 'the system' will protect them from inadvertent re-exposure to a culprit drug. This was the case even among patients highly anxious about the risk of further perioperative reactions. However, this assumption is flawed because there is currently no national system in the UK for alerting healthcare professionals to a perioperative allergy diagnosis; instead, there is reliance on self-reporting by the patient (137, 227, 228). This common misperception contrasts with observed behaviour in patients with more widely recognised allergies (e.g. peanut allergy), where patients are typically pro-active about communicating the diagnosis and ensuring their own safety (208, 233). It is possible that the hospital environment creates a lack of agency for patients, who act as passive recipients of care rather than active participants in ensuring their own safety.

6.5.1 Reflexivity statement

My background, personal and professional experiences all shape the way I approached and conducted this study. Of these, it is my experience as a clinician in the perioperative allergy clinic which is likely to have had the most substantial impact on the design, conduct and analytical process. This experience also underpins my reasons for wanting to conduct research. Over more than 10 years, I have witnessed patients in clinic describing substantial anxiety about the index perioperative event and its implications for their future healthcare safety, whilst at the same time being uncertain about what exactly had happened to them. Their perspectives appear to be heavily influenced by the interactions with healthcare professionals in the immediate aftermath of the event, some of which were inadvertently damaging to the patients' well-being. For example, phrases such as 'you died on the table' have often been used and are upsetting for patients. For others, a complete lack of information given at the time, meant they were unclear about why they had been referred to clinic at all. Further, I observed in clinic that patients sometimes found the diagnosis hard to process and absorb, and I wanted to explore this more deeply to determine potential barriers and facilitators to improving this understanding. Alongside this, I noted that a proportion of patients declined to wear a MedicAlert bracelet or other device for alerting healthcare professionals to their allergy diagnosis, despite being advised to do so. This was difficult to explain given the potential severity of their initial reaction, and I was keen to understand the motives behind this behaviour. The totality of these observations inevitably shaped my views, and meant I was not a neutral observer within the research. My preconceived ideas about patient perspectives and behaviours are likely to have influenced both the development and application of the topic guide for interviews, as well as the analytical process itself.

This issue was flagged from an early stage in the study design with my qualitative supervisor, Dr Rousseau. On balance, we felt the value of having firsthand experience with this patient group and the problems they encounter, outweighed the potential bias and lack of impartiality described above. To help mitigate these issues, Dr Rousseau was involved at all stages of the study, providing invaluable reflections and insights on the conduct and analytical aspects of the research. In addition, I made field notes during some of the earlier interviews,

and used these to reflect on the way I managed and led future interviews. Collectively, this facilitated a more neutral approach to the data and encouraged me to reflect on my potential biases within the analysis. As the study progressed, many of the emergent themes were unexpected and discordant with my prior beliefs, and in addition I noted highly diverse perspectives among patients. This provided some reassurance that any preconceptions I held had minimal impact on the overall conduct of the study or its subsequent conclusions.

6.5.2 Strengths and weaknesses

This study has several strengths. It is the first time that in depth qualitative research has been undertaken in this population. The perspectives of both sexes, across a wide range of ages, and among patients with varying degrees of health literacy were explored, and in particular the voices of older patients and those with limited health literacy, were well represented. Patients were recruited from a relatively large geographical area and a wide range of surgical specialities, providing further variation.

Nevertheless, the small numbers of patients referred to the clinic and limited inclusion of patients from different ethnic background, meant that the study population was not as diverse as I had hoped for. Another area of potential bias was my dual role as a clinician and the primary researcher, discussed earlier in more detail. It is possible that this inhibited patients to talk frankly about their clinic experience, especially if these were negative. Equally, reassurance provided by me prior to their attendance at clinic may have positively affected their subsequent experience of allergy testing. However, most patients were unaware of my dual role, and I noted that all patients gave detailed accounts of their experiences, including negative ones. A further potential limitation was that the study design precluded triangulation of data from other sources (a key feature of some qualitative work) and that our single data source offered a relatively narrow lens for interpretation. In addition, our analysis was open and inductive, rather than grounded in theory as much qualitative work is. This approach allowed us greater flexibility to describe the lived experience of patients, but potentially at the expense of deeper analysis and meaningful interpretation of our findings.

Lastly, a major limitation to our understanding of the patient experience of perioperative allergy is that only patients who were referred to clinic and were willing to participate, are represented in this study cohort. The experience of patients who were not referred despite having suffered a potential reaction, or who failed to attend clinic, may be entirely different. In my clinical experience, such patients fall into three groups. First, patients who are extremely anxious may decline further testing and only be identified and re-referred when pre-assessed for further surgery. Second, a substantial number of patients are not referred for investigation at all. This can reflect a lack of awareness that the intra-operative event might be due to an allergic reaction, or uncertainty about the referral pathway. Third, some patients do not attend simply because they had failed to appreciate or were not told (or did not recall), that they had suffered a potentially serious which required investigation. Again, patients in this category typically attend clinic only after being identified at pre-assessment when further surgery is required – sometimes many years after the index reaction. Any patient who is not investigated is at substantially greater risk from further reactions in the future, and this is an important group to try and reach in future research. The experiences and perspectives of patients who were unwilling to participate in the study are also important to understand. This might represent hesitancy about research more broadly, high levels of anxiety about the reaction itself, or other reasons we were unable to elucidate during this study.

6.6 Conclusions

Perioperative allergic reactions are life-threatening events with far-reaching consequences for mental health and future healthcare safety. Healthcare professionals should be aware that patients are often extremely anxious about the event, and this anxiety can be compounded by a lack of information in the immediate aftermath, and by the use of particular language to describe the event. Being unconscious at the time of the event is protective for some patients, but for many it adds to their anxiety and uncertainty.

The provision of timely, patient-centred information may improve patient understanding and reduce anxiety about the event itself and the proposed allergy testing. Our data also suggest

that provision of patient information would be beneficial after completion of testing, to aid understanding of the diagnosis and its implications for the future healthcare. This includes the need to actively communicate the allergy diagnosis to healthcare providers, rather than leaving it to healthcare systems to flag the allergy up for relevant professionals. With this greater understanding, the risk of future reactions from accidental re-exposure to a culprit drug might be mitigated.

Further research is needed to determine whether these results are generalisable to other patient groups, including those from other ethnic backgrounds and those who, for whatever reason, do not attend clinic.

7 Conclusions and future research

7.1 Drug allergy is source of potentially avoidable harm for surgical patients

Drug allergy labels are a source of harm for surgical patients. The problem is two-fold; patients presenting for surgery with spurious drug allergy labels are precluded from the use of drugs important for effective surgical care, and patients can experience life-threatening allergic reactions to drugs used in the perioperative period. Whilst these two issues appear distinct from one another they are in fact inter-dependent, because it is fear of genuine allergy which drives precautionary and excessive drug allergy labelling. Accurate diagnosis is central to both these problems. Patients presenting for surgery with drug allergy labels rarely have access to timely investigation in order to remove incorrect labels. Among patients who suffer suspected perioperative allergy, a proportion are not referred (or do not attend) for investigation, and among those who are investigated, there may be residual diagnostic uncertainty due to the unique challenges of allergy testing in this setting.

In this thesis, I examined several different aspects of these problems to gain better understanding of the scale of potentially avoidable harm and determine how best to address this. Ultimately, the aim is to improve patient safety through better diagnosis and management of drug allergy. In the sections below, I summarise and contextualise the key findings of my research and outline future research needs.

7.2 Drug allergy labels are associated with increased risk of complications following surgery.

The SAPPHIRE study has confirmed a high prevalence of drug allergy labelling in surgical patients and identified for the first time the scale and nature of the harm associated with such labels. The presence of one or more drug allergy labels was associated with a 24% increased risk of surgical site infections within 30 days after surgery, and a 19% increase in all postoperative complications. The effect sizes are likely to be under-estimated because complications managed exclusively in the primary care setting following discharge were not captured in this study. One of the main drivers for these effects appears to be the increased incidence of postoperative surgical site infection in patients with a penicillin allergy label, the

single most prevalent label among surgical patients. Whilst negative health outcomes have been associated with penicillin allergy in a wide range of patient populations in the literature, the scale of harm in UK surgical patients has been unconfirmed until now. These data provide a powerful signal that the label leads to prescribing of multiple alternative, broad-spectrum antimicrobial agents, resulting in increased surgical site, chest, bloodstream and other infections. Although not captured in this study, the widespread use of broad-spectrum antimicrobials is also a key factor in the development of antimicrobial resistance, a major public health threat in the UK and globally (104-106, 185).

Whilst penicillin allergy labels may account for a substantial proportion of the harms seen in this study, an increase in complications was also seen in patients with other drug allergy labels. A possible mediator for this effect might be the avoidance of high-quality analgesia in the postoperative period in patients with analgesic allergy labels (the second largest category of drug allergy labels in the cohort) or the avoidance of antimicrobials other than penicillin, and use of less effective or more toxic alternatives (86-88).

Overall, it can be concluded that drug allergy labels are common in surgical patients and are associated with harm. My data suggest that penicillin allergy labelling may be a significant driver for this effect, but that other labels are also associated with harm. Further research is required to determine the precise mechanism(s) through which allergy labels negatively impact patient care, and whether delabelling mitigates this risk. Given the size of the UK surgical population, estimated at around 5.5 million patients each year, and global surgical population estimated at more than 330 million per year, there are clearly substantial potential gains to be made in population-level health, and in healthcare costs, by addressing this problem and reducing the burden of drug allergy labels (161-164).

7.3 Current pathways for penicillin allergy delabelling by non-allergists are likely to clinically ineffective and unsafe if implemented routinely

A critical shortage of allergy specialists in the UK means that penicillin allergy testing is essentially unavailable to most patients with this label (15, 89-91). The implementation of routine delabelling by non-allergists is an appealing solution to this problem. Moving allergy

testing out of specialist centres and empowering non-allergists to deliver this would substantially improve accessibility. In recent years, non-allergist delabelling has been developed and researched, as detailed in earlier chapters. Most work reports this as safe, efficacious, and likely to be cost-saving (112, 115, 171, 186, 195, 198-200, 234-237). Over time, we have moved to a position where this widely accepted to be the case, and efficacy of the pathway is assumed to translate to clinical effectiveness.

In 2022, the British Society of Allergy and Clinical Immunology commissioned the development of a national guideline aimed at non-allergists who wish to set-up and deliver delabelling services (125). I led the writing group for this. This guideline details which patients are suitable for non-allergist delabelling, and the conduct and minimum safety standards required for provocation testing. The need for specialist allergy support, during the set-up and ongoing delivery of the service, is emphasised throughout the guideline which was, in effect, a 'recipe' for non-allergist delabelling. Despite this, non-allergist delabelling is not yet embedded into routine NHS care, nor has it been widely adopted outside the UK, save for a limited number of centres where enthusiasts have created local pathways (122, 204). Dependence on individual champions in this way is unlikely to be sustainable in the long term.

The lack of routine implementation raises important questions about why an intervention with apparently substantial benefits for individuals and wider healthcare systems, has not yet been successfully adopted. This may simply reflect the difficulties of changing practice within healthcare, and the time it takes to do so - issues well recognised as barriers to the adoption of new interventions within the NHS and elsewhere (238, 239). However, my clinical and research experience leads me to believe there are other, more fundamental problems which have been under-appreciated or overlooked in the drive to implement non-allergist delabelling. These problems are three-fold, relating to the non-allergist healthcare professionals delivering this pathway, the patients themselves, and the healthcare systems they exist in.

7.3.1 Healthcare professionals

The prevailing view in published literature is that a wide range of non-allergist healthcare professionals, including pharmacists, nurses, physicians, anaesthetists and others, can accurately risk stratify patients and identify those suitable for a penicillin challenge test (119,

121, 192, 240). The SPACE and PASSPORT studies, which overlapped during my fellowship, present novel data at odds with this assumption (113, 179, 180). The SPACE study identified that the non-allergists were often unsure about how to risk stratify patients, made mistakes, and needed help from allergy specialists when confirming patients were suitable for challenge testing. The qualitative analysis suggests that substantial training and experience are required before non-allergist healthcare professionals feel confident in this process. For example, the pharmacists in SPACE had undergone significant prior training in penicillin allergy delabelling during their career and maintained a clinical interest in this, and at least one pharmacist attended drug allergy clinics throughout the study to gain additional experience. By comparison, the research nurses had no prior training or experience and remained reticent about making risk stratification decisions throughout the study, with several expressing anxiety about making a wrong decision. Despite this anxiety, a small number of patients were put forward (at the Leeds site) for challenge testing when they had high-risk allergy histories, or had co-morbidity which should have precluded this. These patients were picked up and excluded on the day of challenge testing by the medical or anaesthetic consultant supervising the test, in line with the study protocol. Nevertheless, this clearly highlights the potential dangers of non-allergist risk stratification.

This aligns closely with findings from the PASSPORT study, which demonstrated that healthcare professionals without specific allergy training lack confidence when risk stratifying patients. This uncertainty was managed by taking an overcautious approach, leading to a large proportion of suitable patients being deemed unsuitable. At the same time, important knowledge gaps led to the misclassification of high-risk patients which, had the study involved subsequent administration of a test dose, might have resulted in avoidable harm. PASSPORT provides novel data about exactly how and why these errors occurred, and the behaviours underpinning non-allergist decision-making. The fundamental issue appeared to be that the assessment of an allergy history was more complex than completing a 'tick box' questionnaire. Patients reported symptoms which required substantial interpretation and did not fit neatly into the available categories within the tool, or they could not recall the index allergic event at all. These issues were most obvious with the history of 'rash' (the most frequently reported symptom), which non-allergists frequently struggling to categorise.

Overall, the data presented in this thesis suggest that risk stratification, the cornerstone of penicillin allergy delabelling, is more complex than previously appreciated. There is an unequivocal need for allergy training and continued input and support from allergy specialists. These findings should perhaps not be surprising, given that many labels are erroneously applied in the first place due to a lack of confidence and knowledge among non-allergists.

Although my data appear to contrast with the published work on non-allergist delabelling, closer inspection reveals that many of these studies were never designed to determine safety or effectiveness, and provide limited or unreliable data on these outcomes. Several key studies involved the retrospective application of a risk stratification tool to score patients already differentiated into low/high risk by an allergy specialist, or even retrospective application of the tool by an allergy specialist themselves (115, 190, 195). Where risk stratification was performed prospectively by non-allergists, these individuals were frequently trained in allergy and had extensive clinical experience, even if allergy was not their primary qualification (116, 186, 200). This includes the PADLES study which I conducted in 2019, in which non-allergy trained nurses performed the risk stratifications, but these were checked by me before challenge testing was performed (120). The study was not powered to detect safety outcomes, and data on incorrect risk stratifications were not collected. Therefore, whilst I demonstrated that non-allergist delabelling was possible, the barriers and risks associated with this were not clear. We cannot extrapolate the findings of any of these studies to determine the safety and reliability of risk stratification by healthcare professionals without allergy expertise, presented with undifferentiated patients, with no support from allergists to 'check the workings out in the margin'. SPACE and PASSPORT provide key data to inform this understanding and guide future iterations of a delabelling intervention.

An additional issue previously noted is that successful delabelling may not result in subsequent use of penicillin. Healthcare professionals and/or patients often remain reluctant to prescribe or take penicillin despite negative allergy testing, with penicillin allergy labels reapplied in up to 63% of patients (120, 241-245). This entirely undermines the intended benefit of delabelling. The reasons for persistent avoidance are incompletely understood, but might include low confidence in the test itself; logistical or system barriers to communication

of the delabelled allergy status; concerns about the medico-legal implications of prescribing penicillin to a patient previously labelled as allergic to this; or the development of de novo reactions following appropriate penicillin administration. Some of these reasons were highlighted in the DALES study, which I conducted in 2020. In this study, fewer than half of nearly 5000 anaesthetists surveyed stated would be happy to prescribe penicillin perioperatively to a patient delabelled by an allergy specialist, using direct penicillin challenge testing (92). Key reasons included a perceived lack of governance and medico-legal framework around delabelling; concerns that an oral dose of penicillin did not clear the patient to receive an intravenous dose; and a belief that skin testing was a mandatory part of allergy testing. For some anaesthetists, simply the fact that the patient had even been labelled as allergic meant they would never be prepared to re-expose them to penicillin. These results suggest very low confidence in the testing process, poor knowledge around allergy, and an anxiety about penicillin allergy which is, arguably, disproportionate. The ALABAMA study found that both GPs and patients were reluctant to follow the advice from allergy clinic when a patient had been delabelled, and identified behaviour change techniques which were subsequently adopted within an intervention package designed to improve prescribing of penicillins after delabelling (127, 229). This appeared to be successful in reducing the rate of re-labelling in the 12 months after delabelling (paper under review at the time of writing). Strategies such as this are likely to be critical to the success of any delabelling intervention, but substantially more research is needed to fully understand this problem.

7.3.2 Patients

Most of the published work, including some of my own, describes high uptake of delabelling among patients and low levels of anxiety about allergy testing (116, 120, 192, 198, 246). However, the findings from SPACE and PASSPORT do not support this assessment. In SPACE, 60% (273/458) patients declined to take part in the study, and of those who initially agreed, some later dropped out prior to challenge testing (up to 18% but exact number not recorded). A substantial limitation to study design was that the reason for declining to participate was not recorded. It is possible that patient refusal stemmed from reticence about participation in research, rather than the allergy testing itself. We noted particularly low uptake among

patients from ethnic minority backgrounds, with 85% patients being white, but have no data to understand the barriers to recruitment. In PASSPORT, 70% (317/456) of potentially eligible patients declined to participate or were uncontactable, although the reasons for this were not recorded. Overall, the data suggest that substantially fewer than half of patients with a penicillin allergy label would agree to delabelling if this were implemented within routine care.

In addition to high rates of patient refusal, we encountered much higher rates of ineligibility among patients than previously reported (121, 196, 234, 247). In SPACE, 54% (534/992) were ineligible or uncontactable. The primary reasons for this were being clinically unstable or unsuitable. In PASSPORT, our only exclusion criteria were unwillingness or inability to consent to participation and therefore meaningful parallels cannot be drawn. However, we can surmise from these studies that overall, at least 70-80% of patients with a penicillin allergy label would be unwilling or unable to participate in any future interventional delabelling trial. If delabelling were introduced as routine care this figure might increase, but we currently lack supporting data for this hypothesis.

The data from SPACE and PASSPORT align with previous work in only one key area. The proportion of patients risk stratified as 'low-risk', at 56% (104/185) and 49% (49/101) respectively, is broadly aligned with estimates in the literature of between 40%-60% (189, 248, 249) Nevertheless, when accounting for the small proportion of patients who progress to risk stratification, we might anticipate that the overall number of patients determined to be low risk and suitable for challenge testing would be less than 10% of the overall population of patients with this label. In the UK, this equates to around 60,000 patients per year based on 12% of a total surgical population of 5,000, 000 being labelled as penicillin allergic (92, 162). Epidemiological work I conducted in 2020 suggests that only 20% of this population are likely to require penicillin-based prophylaxis for surgery, approximately 12,000 patients (92). Whilst there may be benefit for these individuals, the impact on antimicrobial resistance patterns and overall healthcare costs remains unknown and may be somewhat marginal.

7.3.3 Healthcare systems

Implementation of non-allergist delabelling requires practical solutions to some of the logistical, digital and systems barriers that exist around this problem. These include the timely identification of patients for delabelling (particularly in the surgical setting); difficulty around amending or removing an allergy label from the electronic record; difficulty in communicating the updated allergy diagnosis to primary care; and prevention of re-labelling (92, 236, 241, 250). The SPACE and PASSPORT studies identified that timely identification of surgical patients is problematic, in part reflecting recent changes to pre-operative assessment pathways. Despite long wait times, patients are typically listed within 2-4 weeks of planned surgery, leaving limited time for allergy testing. These issues represent a barrier to future delabelling interventions and are discussed below in 'Future Research'.

7.3.4 Further research is needed before non-allergist delabelling can be implemented into routine care in the NHS

Overall, we can conclude that despite a widespread assumption that non-allergists can lead and deliver penicillin allergy delabelling, there are substantial barriers which limit the effectiveness and safety of this pathway. Only a small proportion of patients are likely to be willing and able to undergo testing, with particularly low engagement observed in patients from ethnic minority and deprived backgrounds. Non-allergists lack confidence in delabelling unless they have received substantial training and experience, resulting in precautionary exclusion of low-risk patients from challenge testing alongside potential harm in high-risk patients. Even after successfully delabelled, subsequent use of penicillin is limited by persistent anxiety about the label among both patients and healthcare professionals. In this context, the successful implementation of delabelling programs delivered by non-allergists remains unlikely at present. The research needed to tackle these problems will be informed in part by the findings of SPACE and PASSPORT and is described later in this chapter.

7.4 Patients who suffer suspected perioperative anaphylaxis are at risk of significant and potentially avoidable harm

The qualitative study presented in this thesis investigated patients with suspected perioperative allergy and described the experience, views, and behaviours of this small but important patient group. To my knowledge, there has been no previous work to inform our understanding of the patient perspective on these reactions or its implications in terms of future healthcare interactions. The key findings were that being unconscious during the reaction (as is most often the case) had a substantial impact on how the event was interpreted and processed by the patient. Their 'absence' creates a form of cognitive dissonance, because by the time patients are aware of what had happened the symptoms of their reaction have largely disappeared. For some, this made it harder to accept what had happened or understand the severity of the reaction, whilst for others the lack of awareness appeared protective. Following the event, many patients remained highly anxious, to the point of limiting their daily activities and hobbies in order to avoid the need for healthcare and surgery. This was debilitating for several patients. However, others described inappropriately low levels of anxiety, and were unconcerned about the event. The interaction of serious physical health issues or caring responsibilities with the perioperative reaction generally appeared to diminish the importance of the event for patients.

The consistent theme in these rather contradictory data, was the critical importance of providing better patient information at the time of the reaction, and in the period between the reaction occurring and being seen in clinic. Much of the anxiety described by patients was caused by a lack of understanding about the event and its implications, either because they were not told, or could not remember information provided in the immediate recovery period. For some patients, the anxiety related to allergy testing itself, which again could be relatively easily addressed with high quality information resources. For other patients, clear information may be critical to ensuring they understand the importance of attending clinic to be investigated.

Following investigation, it became clear that whilst a small minority of patients appeared to completely understand their diagnosis and how to manage this during future healthcare interactions, a greater proportion remained uncertain and displayed behaviours which would

substantially increase their risk of future reactions. This included entirely misunderstanding or misremembering the diagnosis, having low confidence in the diagnosis, or finding it difficult to recall specific drug names for some of the commonly used perioperative drugs (for example the neuromuscular blocking drugs). These issues were compounded when there was diagnostic uncertainty at clinic, particularly if this resulted in a diagnosis of potential allergy to multiple drugs. A common theme was that the provision of high-quality, patient-friendly information to help explain their diagnosis would be beneficial.

The most striking finding from my work was that a high proportion of patients appeared ambivalent about the need to communicate their diagnosis to future anaesthetists and other healthcare professionals. Even among those who understood their diagnosis, there was a perception that responsibility for taking steps to prevent re-exposure to the drug(s) lay with healthcare professionals or systems. This flawed assumption leaves patients at risk of future reactions, particularly if they move regions or undergo emergency surgery, where there may be less time for pre-assessment. In truth, anaesthetists rely almost exclusively on patients reporting their previous reactions; systems to pick this up and alert anaesthetists are fragile or non-existent. These data highlight the well-recognised need for national-level reporting and alert systems.

Overall, this study demonstrated that suspected perioperative allergic reactions have long-lasting and often life-changing implications for many patients. There is a clear, unmet need for high-quality patient information following the event and prior to clinic investigation. This should take the form of co-designed leaflets, videos and other resources, aiming to reduce the fear and anxiety experienced by patients. Post-clinic information is also essential, to ensure patients are aware of the need to communicate their diagnosis in a pro-active way, rather than trusting in the system to alert the next anaesthetist.

7.5 Strengths and limitations

The main strength of this work is that the findings are novel and likely to be impactful. I have provided the first estimate of the nature and extent of harm associated with drug allergy labels in a generalisable, UK surgical population, and the first work to explore the patient perspective on the impact of perioperative allergic reactions. I have also provided the first

detailed assessment of the performance of a penicillin allergy risk stratification tool in the hands of non-allergists used in unselected surgical patients without allergist oversight, and the first multi-centre feasibility study of non-allergist delabelling in surgical patients. For the SAPPHIRE, PASSPORT and SPACE studies, the multi-centre nature of the work increases their generalisability and is a key strength. Across all studies, data completion rates were very high, and validation of source data increases confidence in the findings.

There are important limitations to all the studies presented in this thesis. In SAPPHIRE, the selection of only six surgical procedures means that associations observed between drug allergy labels and surgical complications might not exist for other types of surgery. Additionally, there is a risk that complications were under-reported given the lack of primary care data in the analysis, resulting in under-estimation of the true extent of harm associated with drug allergy labels. Further, it is important to note that the data presented demonstrate association but not causality. There are biologically plausible mechanisms for why the avoidance of important drugs might result in worse outcomes, but these causal inferences are unproven. Further research is required to elucidate the exact mechanism(s) underpinning this observed association, and to moreover to determine whether removal of drug allergy labels leads to improved outcomes. Lastly, as for all observational research, there may be unmeasured confounders which have introduced bias.

In the qualitative study of patients who experience suspected perioperative allergy, the small sample size and limited diversity of the cohort provides only a narrow range of possible views, which must be confirmed (or refuted) in further research. Similarly, the relatively small sample sizes and limited patient diversity in the SPACE and PASSPORT cohorts, limit their generalisability.

Lastly, my role as a both a clinician and researcher may have had a significant impact on the qualitative aspects of this research. Whilst my experience brought a detailed understanding of the likely issues at hand, it also meant I held prior views and expectations about what the research might show. This is likely to have shaped the conduct of both the interviews themselves and subsequent interpretation of the data for these more subjective analyses.

7.6 Future research needs

Overall, my findings provide a first step towards greater understanding of the scale of harm of drug allergy in surgical patients and how to overcome the barriers to improving care in this population. However, further research is needed in order to solve these problems.

7.6.1 Reducing harm for incorrect drug allergy labels in surgical patients

7.6.1.1 Developing pathways for non-allergist penicillin allergy delabelling

Penicillin allergy is the exemplar for the wider problem of spurious drug allergy labelling in surgical and other patient populations. I have focussed on penicillin in this section since this is the most common label, but the principles are likely to be applicable across all drug allergy labels.

The barriers and enablers to non-allergist penicillin delabelling are central to much of this thesis. A key component of this process is the selection of patients suitable for direct challenge testing using a risk stratification tool. I have demonstrated this to be inaccurate, unreliable and potentially unsafe in the hands of non-allergists without close oversight from specialists in allergy. However, there are other substantial barriers to effective implementation, some of which are highlighted in SPACE and PASSPORT. These include: low levels of patient engagement; lack of pathways to identify patients at an appropriate time to be offered delabelling; lack of trust in the results of delabelling; relabelling of patients through poor communication between and within electronic healthcare systems; and limited evidence of overall cost savings. To address these issues in the surgical population, the following broad areas of research should be prioritised:

I. *Qualitative research in surgical patients who do not wish undergo delabelling.*

   To date, qualitative studies have only included cohorts of patients who have chosen to be considered for delabelling. In reality, at least half of surgical patients with the label decline delabelling, but the reasons for this are unknown. Patients from ethnic minority backgrounds are consistently under-represented, as are those with poor health literacy. For provision of delabelling to be equitable, it is vital to understand why some patients decline this intervention. Reasons might include distrust of

healthcare services, fear about receiving penicillin, lack of time ahead of surgery, or lack of awareness about the harms associated with avoiding penicillin in the perioperative period.

II. *Determining processes for the timely delabelling of surgical patients*.

Patients are currently offered a range of interventions ahead of planned surgery, aimed at modifying risk factors known to increase the likelihood of poor outcomes. For example, smoking cessation programmes; correction of iron deficiency anaemia; improved diabetic control; and optimisation of respiratory or cardiovascular disease. Removal of incorrect penicillin allergy labels is a further intervention which could be offered as part of 'pre-optimisation' (as it is known), but the ideal process for identifying suitable patients and organising testing ahead of surgery have yet to be elucidated.

III. Prevention of relabelling.

Relabelling is thought to occur in up to 40-50% of patients, and fundamentally undermines the delabelling process. Few solutions to this have been successfully trialled to date. Digital solutions might include improved systems for recording a negative challenge test; 'pop up' reminders about the patient's delabelled status; and the confirmation of this status on surgical operating lists. Other solutions might focus on how to empower individuals themselves – for example, the use of wallet cards confirming they have been delabelled and better patient education.

IV. Prevention of incorrect labelling

Improved education and training around allergy are critically important to reducing the number of incorrect allergy labels. Digital solutions should also be explored, such as improved processes for recording adverse drug reactions and the use of 'pop-ups' in electronic records to highlight possible incorrect labels.

7.6.2 Improving the care of patients with suspected perioperative allergy

My research has highlighted the inadequacies of current care in the NHS for this patient group, and informs the research needed to address these problems. Specifically, there is a need to:

I. Develop, through co-design with patients, a range of resources detailing the key information about the suspected reaction, the process of allergy testing, and the implications of the diagnosis given in allergy clinic. The impact of these resources on patients will need to be explored through future qualitative research.

II. Develop a national database for cases of perioperative allergy, to facilitate timely communication of test results irrespective of where and when a patient presents for future surgery, to reduce the likelihood of accidental re-exposure to a culprit drug.

III. Improve diagnostic certainty for patients investigated for perioperative allergy. This would include validation of current testing modalities, as well as the development and validation of novel diagnostic tools, such as basophil and mast cell activation testing. The routine use of challenge testing for NMBAs, induction agents and hypnotics facilitates both these aims, but further research is needed to determine the ideal protocol for testing. Issues which require consensus and standardisation include the selection of appropriate patients; the use of full or partial doses for challenge testing, and the appropriate expertise of personnel conducting the test.

IV. Improve our understanding of the underlying mechanism(s) and causes of perioperative hypersensitivity. This will include research exploring pathways of mast cell and basophil activation and determining whether these are modifiable for particular drugs and/or patients. In addition, the role of genetic risk factors in perioperative hypersensitivity must be explored, such as the presence of hereditary alpha tryptasaemia or specific HLA associations. Such work is in its infancy in the field of drug allergy, and particularly in perioperative allergy.

7.7 Summary

I have demonstrated in a UK surgical population that the presence of one or more drug allergy labels in the patient record substantially increases the risk of post-operative complications

and identified the key mediators for this harm. These data provide key insights into the avoidable patient harm associated with drug allergy labelling, and will inform the design of future research aimed at reducing this harm through targeted, pre-operative drug allergy delabelling. I have also demonstrated that despite a widespread acceptance of the benefits of penicillin allergy delabelling by non-allergists, this is both clinically ineffective and unsafe when risk stratification tools are used by non-allergists among unselected surgical patients without substantial oversight from allergy specialists. I have determined the main barriers to implementation and future success of non-allergist delabelling as a pre-operative intervention, and provided key data to inform future research into overcoming these barriers. Lastly, I have highlighted the extent to which suspected perioperative allergic reactions lead to long-term psychological harm in patients, irrespective of their eventual allergy diagnosis, and shown that patients remain at increased, avoidable risk from future reactions. This will inform the design of a program of work to improve patient understanding, reduce anxiety, and mitigate future risk. These findings mark a step change in our understanding of the impact of drug allergy among surgical patients and highlight the ways in which we might increase the safety and effectiveness of surgical care.

8 Appendices

8.1 Appendix 1: Statistical analysis plan for SAPPHIRE study

1. Objectives

- To identify any associations between the presence of a drug allergy label(s) and the incidence of surgical site infections within 30 days after surgery.
- To describe any associations between presence of a drug allergy label and the following secondary outcomes:
    - Number of antimicrobials to treat an infection
    - Incidence of antimicrobial side effects within 30 days after surgery
    - Incidence of postoperative infection within 30 days after surgery
    - Incidence of all postoperative complications within 30 days after surgery
    - Mortality within 30 days after surgery
- To describe any associations between the presence of penicillin allergy labels and non-penicillin allergy labels and the following outcomes:
    - Surgical site infections within 30 days after surgery
    - Infective complications within 30 days after surgery
    - Postoperative complications within 30 days after surgery
    - Number of antimicrobial agents used within 30 days after surgery

2. Sample size calculation

The sample size for the SAPPHIRE observational cohort study was calculated using the "simsam" package in STATA (version 17.0), which employs a simulation-based approach. An initial recruitment target of 13,720 patients was based on an estimated 10% prevalence of allergy labels in the population. However, a revised literature review indicated that the prevalence of allergy labels is approximately 29%, leading to an adjusted sample size requirement for the secondary outcome analysis of 4,732 participants to achieve 80% power. The outcome focuses on the association between allergy labels (a binary exposure) and postoperative complications. The following assumptions were made for this analysis:

- **Incidence of complications in the exposed group (patients with an allergy label)**: 15%.
- **Incidence of complications in the unexposed group (patients without an allergy label)**: 10%.
- **Power** (β): 80% (1-β = 0.80),
- **Significance level** (α): 5% (two-sided test).

Using a logistic regression model, the sample size required to detect this association is **1,372 patients**. Since only 29% of the cohort is expected to have an allergy label, the total cohort size required to ensure sufficient power for this analysis is **4,732 patients**.

3. Exposures and outcomes

Primary analysis

Exposure

(3) Presence of any drug allergy label

Primary outcome

- Surgical site infection within 30 days after surgery

Secondary analyses

Exposure (1)

- Presence of any drug allergy label

Outcomes

- Number of antimicrobials to treat an infection
- Incidence of antimicrobial side effects within 30 days after surgery
- Incidence of postoperative infection within 30 days after surgery
- Incidence of all postoperative complications within 30 days after surgery
- Mortality within 30 days after surgery

Exposure (2)

- Types of allergy label (penicillin and non-penicillin)

Outcomes

- Surgical site infection within 30 days after surgery
- Number of antimicrobials to treat an infection
- Incidence of postoperative infection within 30 days after surgery
- Incidence of all postoperative complications within 30 days after surgery

4. Statistical analysis

Data Cleaning

A thorough data cleaning procedure will be implemented as follows:

- The database has been designed to minimise data entry errors by having various validations measures in place. The e-CRF provides a warning message and asks the user to confirm the value of any data entered which lie outside the pre-determined validity range (hard and soft ranges), e.g. if haemoglobin is less than 30 g/L or age greater than 100 years.
- Data will be verified for duplicates and removed.

Handling of missing data

Patients missing primary outcome measure data will be excluded from the analysis. For patients with <5% of data missing we will perform multiple imputation.

Characteristics of the cohort

The following characteristics will be presented for all patients:

- Age, mean (SD) and median (IQR)
- Gender, n (%)
- ASA grade (I, II, III, IV), n (%)
- Risk factors (obesity, antibiotics for pre-existing infection, immunosuppressant disease, active malignancy, current smoker, diabetes mellitus, poor nutritional state, immunosuppressant drugs, frailty, know carrier of resistant organism, chemo or radiotherapy), n (%)
- Anaesthetic technique (general, spinal, epidural, other regional), n (%)
- Surgical procedure (colorectal resection, elective Caesarean section, abdominal hysterectomy, vaginal hysterectomy, primary hip replacement, primary knee replacement, transurethral resection of prostate, transurethral resection of bladder tumour, open surgery for closed long bone fracture), n (%)
- Wound contamination, n (%)
- Duration of surgery (<2, 2-<4, 4-<6, >6 hours), n (%)
- Proportion of all patients with one or more drug allergy label(s) (%)

The following characteristics will be presented for patients reporting drug allergy:

- Category of drug allergy (any drug allergy; any antimicrobial allergy; penicillin allergy) n (%)

Analysis

Descriptive analysis:

A summary of descriptive data stratified by presence or absence of drug allergy label and further stratified by the presence or absence of an antimicrobial allergy label, including a penicillin allergy label. Continuous data will be presented as mean (SD) or median (IQR) and categorical data will be presented as number (%). Hypothesis testing will not be conducted on baseline data.

Primary analysis

Binary outcomes:

1. Surgical site infection within 30 days after surgery

To investigate associations between the main exposure of interest (presence of drug allergy label) and the primary outcome, we will perform a mixed effects negative binomial regression or a mixed effects logistic regression model with a random intercept for site, adjusted by all other recorded variables one at a time. These effect estimates will be compared with the crude effect estimates for the main exposure. Finally, a mixed effects negative binomial model will be fitted to estimate the effect of the exposure of interest on the outcome, adjusted for any confounders. Covariates will be included in the model based on clinical plausibility using a forced simultaneous entry approach.

The baseline risk factors we will consider are as follows: age, gender, surgical procedure, current smoker, diabetes mellitus, ASA, wound contamination, duration of surgery, active cancer, liver cirrhosis, obesity, and frailty. For the analysis of mortality we will also include hypertension, heart failure, coronary artery disease, peripheral vascular disease, asthma/COPD as covariates.

Secondary analyses

Binary outcomes:

1. Incidence of antimicrobial side effects within 30 days after surgery
2. Incidence of postoperative infection within 30 days after surgery

3. Incidence of all postoperative complications within 30 days after surgery
4. Mortality within 30 days after surgery

Count outcomes:

1. Total number of antimicrobial agents used from recruitment to 30 days after surgery

a) The analysis will be repeated using the presence of an antimicrobial drug allergy label(s) as the exposure of interest, and the outcome of incidence of surgical site infection.
b) The analysis will be repeated using the presence of an antimicrobial drug allergy label(s) as the exposure of interest, and the outcome of incidence of infective complications.
c) The analysis will be repeated using the presence of an antimicrobial drug allergy label(s) as the exposure of interest, and the outcome of incidence of all postoperative complications.
d) The analysis will be repeated using the presence of an antimicrobial drug allergy label(s) as the exposure of interest, and the outcome of morality.
e) The analysis will be repeated using the presence of an antimicrobial drug allergy label(s) as the exposure of interest, and the outcome of total number of antimicrobial agents used

Sensitivity analysis

Binary outcomes:

- Surgical site infection within 30 days after surgery
- All complications within 30 days after surgery
- All infective complications within 30 days after surgery

Count outcomes:

- Total number of antimicrobial agents used from recruitment to 30 days after surgery

Categorical outcome:

- Category of drug allergy label(s) reported by patient

I. The analysis will be repeated using the presence of a penicillin allergy label as the exposures of interest and the outcomes of interest as:
   a) Surgical site infection
   b) Incidence of all complications
   c) Incidence of all infective complications
   d) Total number of antimicrobial agents used
II. The analysis will be repeated using the category of drug allergy label as the exposure of interest, and the outcome of all complications

8.2 Appendix 2: Data collection form for SAPPHIRE study

NHS
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NHS Trust

SAPPHIRE Study Case Report Form

Month/year of surgery: |__|__|__|/|__|__|__|__| Rockwood Frailty Score: |__|__|

Age (yr): ☐ 18-27 ☐ 28-37 ☐ 38-47 ☐ 48-57 ☐ 58-67 ☐ 68-77 ☐ 78-87 ☐ 88-97 ☐ 98-107

Sex ☐ M ☐ F ASA ☐ I ☐ II ☐ III ☐ IV

Current smoker: ☐ Y ☐ N

Risk factors (*tick all that apply*):

☐ None
☐ Obesity
☐ Diabetes Mellitus
☐ Liver cirrhosis
☐ Active cancer
☐ Heart failure
☐ Coronary artery disease
☐ Hypertension
☐ Stroke
☐ Asthma / COPD
☐ Peripheral vascular disease

Patient reported drug allergy or sensitivity ☐ Y ☐ N

If yes, please specify drug(s): _____

Laboratory tests (no more than 28 days *before* surgery):

Haemoglobin: ☐☐☐ g/L Creatinine: ☐☐☐ µmol/L

Anaesthetic technique (*tick all that apply*):

☐ General ☐ Spinal ☐ Epidural ☐ Regional nerve block ☐ Sedation

If general anaesthesia: ☐ Volatile ☐ TIVA

Surgical procedure category (*single best answer*):

☐ Colorectal resection
☐ Primary hip/knee replacement
☐ Caesarean section
☐ Hysterectomy (vaginal or abdominal)
☐ Trans-urethral resection of prostate or bladder tumour
☐ Internal fixation of a closed long bone fracture (upper/ lower limb)

Open surgical technique used ☐ Y ☐ N

Wound contamination during surgery ☐ Y ☐ N

Duration of surgery |__|__| : |__|__|
HR MINS

Prophylactic antimicrobial use:

Were antimicrobials given before/ during / after to *prevent* an infection after surgery

☐ Y ☐ N

Prophylactic antimicrobials administered (*tick all that apply*)

Before induction of anaesthesia ☐ Y ☐ N

Before start of surgery ☐ Y ☐ N

Further antibiotics during surgery ☐ Y ☐ N

After surgery ☐ Y ☐ N

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Which drugs were used (*tick all that apply*):

☐ Benzylpenicillin	No: of doses |__|__|	☐ Cefuroxime	No. of doses |__|__|
☐ Ceftriaxone	No: of doses |__|__|	☐ Ciprofloxacin	No: of doses |__|__|
☐ Clindamycin	No: of doses |__|__|	☐ Co-amoxiclav	No: of doses |__|__|
☐ Flucloxacillin	No: of doses |__|__|	☐ Gentamicin	No. of doses |__|__|
☐ Metronidazole	No: of doses |__|__|	☐ Piperacillin/ Tazobactam (Tazocin)	No. of doses |__|__|
☐ Teicoplanin	No: of doses |__|__|	☐ Other (please specify): _____	No: of doses |__|__|

Level of care on the first night after surgery:

☐ Critical care level 3 (ITU) ☐ Critical care level 2 (HDU) ☐ Enhanced care level 1 (PACU)
☐ Ward care level 0 ☐ Home

Therapeutic antimicrobial use:

Were antimicrobials given to treat a suspected/ proven infection within 30 days after surgery

☐ Y ☐ N

Which drugs were used (*tick all that apply*):

☐ Amoxicillin	No: of doses |__|__|	☐ Azithromycin	No. of doses |__|__|
☐ Aztreonam	No: of doses |__|__|	☐ Benzylpenicillin	No. of doses |__|__|
☐ Ceftriaxone	No: of doses |__|__|	☐ Cefuroxime	No. of doses |__|__|
☐ Cephalexin	No: of doses |__|__|	☐ Ciprofloxacin	No. of doses |__|__|
☐ Clindamycin	No: of doses |__|__|	☐ Co-amoxiclav	No. of doses |__|__|
☐ Co-trimoxazole	No: of doses |__|__|	☐ Erythromycin	No. of doses |__|__|
☐ Flucloxacillin	No: of doses |__|__|	☐ Gentamicin	No. of doses |__|__|
☐ Imipenem	No: of doses |__|__|	☐ Metronidazole	No: of doses |__|__|
☐ Meropenem	No: of doses |__|__|	☐ Piperacillin/ Tazobactam (Tazocin)	No. of doses |__|__|
☐ Rifampicin	No: of doses |__|__|	☐ Teicoplanin	No. of doses |__|__|
☐ Trimethoprim	No: of doses |__|__|	☐ Vancomycin	No. of doses |__|__|
☐ Other (please specify): _____		No. of doses |__|__|	

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Outcomes within 30 days of surgery:

Patient status: ☐ **Alive** ☐ **Dead** **Number of days after surgery death occurred: |__|__|**

Infections:

	I	II	III	IV	V	None
Superficial surgical site	☐	☐	☐	☐	☐	☐
Deep surgical site	☐	☐	☐	☐	☐	☐
Organ space	☐	☐	☐	☐	☐	☐
Pneumonia	☐	☐	☐	☐	☐	☐
Urinary tract	☐	☐	☐	☐	☐	☐
Bloodstream	☐	☐	☐	☐	☐	☐
Intracranial/ Meningitis/ Ventriculitis	☐	☐	☐	☐	☐	☐
Infection, source uncertain	☐	☐	☐	☐	☐	☐

Number of days after surgery the first postoperative infection occurred: |__|__|

* Please grade Clavien-Dindo scale as follows:

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diuretics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.

II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.

III. Requires surgical, endoscopic or radiological intervention.

IV. Life-threatening complication (including CNS complication, but excluding transient ischaemic attack) requiring critical care admission

V. Death

Suspected or confirmed allergic reaction within 30 days of surgery:

Suspected or confirmed allergic drug reaction: ☐ **Y** ☐ **N**

If known, what was the suspected cause of the allergic reaction: _____ ☐ **Unknown**

If yes day of reaction (day of surgery = d0): _____

Grade* ☐ **I** ☐ **2** ☐ **3** ☐ **4**

* Please grade suspected or confirmed allergic reaction as follows

- Grade 1: Cutaneous signs: erythema, urticaria, angioedema
- Grade 2: Moderate multivisceral: cutaneous +/- hypotension +/- tachycardia +/- cough, dyspnoea +/- digestive signs
- Grade 3: Severe mono- or multivesicular signs: cardiovascular collapse, tachycardia or bradycardia +/- arrhythmia +/- bronchospasm +/- digestive signs
- Grade 4: Cardiac arrest

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Other outcomes within 30 days after surgery:

	I	II	III	IV	V	None
Acute kidney injury	☐	☐	☐	☐	☐	☐
Anastomotic leak	☐	☐	☐	☐	☐	☐
ARDS				☐	☐	☐
Diarrhoeal illness (any cause)	☐	☐	☐	☐	☐	☐
Hearing loss (any cause)	☐	☐	☐	☐	☐	☐
Tinnitus	☐	☐	☐	☐	☐	☐
Vertigo	☐	☐	☐	☐	☐	☐
Myocardial infarction	☐	☐	☐	☐	☐	☐
Postoperative bleed	☐	☐	☐	☐	☐	☐
Pulmonary embolism	☐	☐	☐	☐	☐	☐
Stroke	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐

Any treatment initiated by General Practitioner: ☐ Y ☐ N

Laboratory tests (within 30 days *after* surgery): ☐ Y ☐ N

If YES, please complete below:

Haemoglobin*: ☐☐☐ g/L **Creatinine**:** ☐☐☐ µmol/L

* please use the lowest value recorded

** please use the highest value recorded

Details of hospital stay:

Total duration of the level 2 critical care stay within 30 days after surgery |__|__|

Total duration of the level 3 critical care stay within 30 days after surgery |__|__|

Total duration of hospital stay within 30 days after surgery |__|__|

8.3 Appendix 3: Clinical scenarios used for healthcare professional training in SPACE study

Age **Gender** **Ethnicity**	67years Male British
Past medical history and drug history	ITP, Crohn's, asthma, T2DM, OA right ankle. Regular prednisolone 15mg OM, dose doubled recently for worsening of asthma
Symptoms/signs of index reaction	Throat / tongue swelling, admitted to hospital for adrenaline, chlorpheniramine and hydrocortisone. Patient unable to recall all details of the reaction or the penicillin related to this reaction. Index reaction may have occurred approx. 4 years ago. No rash No previous challenge or course of a penicillin related antibiotic since the index reaction.
Time elapsed since index reaction	4 years approx.

Age **Gender** **Ethnicity**	50 year old Male white

Past medical history and drug history	COPD – well controlled, HTN and T2DM. Intermittent spontaneous urticaria
Symptoms/signs of index reaction	30 years ago, he had a 7 day course of amoxicillin for a chest infection. On day 10 he reports an itchy rash on his arms, lower limbs and chest. No red flag symptoms related to the rash reported.
Time elapsed since index reaction	30 years

Age **Gender** **Ethnicity**	26 year old Female White
Past medical history and drug history	Recurrent tonsilitis
Symptoms/signs of index reaction	Multiple courses amoxicillin over last 2 years. On last course (3 months ago) developed rash. Itchy, hives, all over body. No swelling, breathing difficulties or other features, but patient reports it was very bad. Didn't go to hospital, took antihistamines and it settle within 3 days. Rash developed on day 2 of the course, stopped taking
Time elapsed since index reaction	3 months

Age **Gender** **Ethnicity**	83 years Male White British
	IHD

Past medical history	Mild COPD
Symptoms/signs of index reaction	He was prescribed penicillin more than 20 years ago. He is unsure why he was given penicillin but a few hours after taking it his fingers swelled on both hands. His GP changed his antibiotic and the swelling subsided, he did not need to come to hospital and was not given any treatment for his reaction. He cannot recall the name of the penicillin
Time elapsed since index reaction	20 years

Age **Gender** **Ethnicity**	66 year old Female Asian
Past medical history and drug history	Breast cancer, type 2 DM, mild ischaemic heart disease -well controlled. No COPD but is a smoker.
Symptoms/signs of index reaction	Rash with penicillin. Happened at least 20 years ago, doesn't have great recall. Sure that she didn't go into hospital, thinks the GP gave her some cream. Unsure when the rash developed in relation to the first dose. Thinks also had some tingling/swelling of her lips.
Time elapsed since index reaction	>20 years ago

8.4 Appendix 4: Statistical analysis plan for pre-surgical patients in the SPACE study

Data collection

All data were entered onto RedCap and held by Leeds Teaching Hospitals NHS Trust, prior to transfer of the final dataset to Birmingham at the end of the study. These data were used for my post-hoc analysis of the pre-surgical patient data, and included:

- Descriptive data for the screened population and the consented population, comprising: age, sex, ethnicity (white/non-white)
- Proportion of screened patients who consented to participate, n (%)
- Reasons for declining participation
- Time taken to consent and risk stratify patients, minutes
- Proportion of consented patients who were low risk, n (%)
- Proportion of low-risk patients who consented to undergo DPT, n(%)
- Proportion of low-risk patients who successfully completed DPT, n (%)
- Number of adverse events related to DPC

Analysis

The majority of analysis will be descriptive, since the small sample size precludes meaningful inferential analysis. The analysis will be performed using STATA V17.0.

8.5 Appendix 5: Topic guide for patient interviews in qualitative arm of the SPACE study

Setting the scene: Remind about the de-labelling programme and that the reported penicillin allergy may be serious/severe or a milder reaction.

1. Opening questions

a) How and when you did you find out that you are/might be allergic to penicillin?

b) What do you know about penicillin allergies?

Prompt for knowledge of:

- Prevalence
- Health effects/ effect on treatment decisions
- Diagnosis including formal testing in allergy clinic

c) How has being allergic to penicillin affected you?

2. Oral penicillin challenge

a) When contacted by members of the research team, you declined/agreed to undergo a test to see if you are allergic to penicillin. What led to you this decision?

Prompt for:

- Perceptions/knowledge of specific health risks
- General health fears/anxieties including the immediate clinical context
- Other relevant experiences and factors (e.g. family history, previous experiences of health care, media exposure)
- Levels of certainty/doubt in the decision

3a. Questions for those declining the intervention

a) What, if anything, might have changed your decision to undergo a test?

3b. Questions for those accepting the intervention

a) How was your experience of the direct oral penicillin challenge?

b) Have you told your GP about the change in your allergy status? (prompt for how they might respond to future questions about their allergy status)

c) Would you advise us to change any aspect of how/when the challenge was carried out? (if yes, please elaborate)

d) What would your advice be to others who have or may not have a penicillin allergy? Would you recommend a direct oral penicillin challenge?

4. **Closing questions**

a) Is there anything else you would like to add on this subject?

b) Do you have any questions for the research team?

8.6 Appendix 6: Topic guide for healthcare professional focus groups in SPACE study

Participants: stakeholders including prescribers, pharmacists and nurses involved in antimicrobial stewardship, and managers and senior clinicians

Pre-amble

Brief explanation of the de-labelling intervention and purpose of the focus group: to explore what factors influence extent and nature of implementation, and determine potential enablers and barriers.

Questions for discussion

1. What are your initial thoughts on the intervention?

2. How do you think the intervention has/will affect you/your role?

3. How do you think the intervention has/will affect the unit/organisation?

3. What factors help/hinder introduction of the new way of working? What strategies might help with ongoing implementation?

Prompt for discussion of:

- Knowledge: e.g. of the issue, intervention
- Skills: e.g. adopting new way of working, individually and collectively
- Memory/attention: e.g. given other work pressures
- Professional roles and beliefs about capabilities
- Beliefs about consequences: e.g. for patients and the organisation
- Motivation and goals e.g. personal and the organisation
- Context and resources: e.g. organisational culture, critical events, finance
- Social influences: e.g. norms, power, group identity
- Emotion: e.g. fear, stress
- Behavioural regulation: e.g. governance, procedures

8.7 Appendix 7: PASSPORT Agreement Study Risk Stratification Tool

PART A: What is the name of the penicillin that caused the allergic reaction?		
Select all that apply*	**Yes**	**No**
Penicillin V	☐	☐
Penicillin G	☐	☐
Ampicillin	☐	☐
Amoxicillin	☐	☐
Co-amoxiclav (also known as Amoxicillin or Augmentin)	☐	☐
Flucloxacillin	☐	☐
Co-fluampicil (also known as Flucloxacillin and Ampicillin)	☐	☐
Piperacillin/Tazobactam (also known as Tazocin)	☐	☐
Temocillin	☐	☐
Pivmecillinam (also called Amdinocillin)	☐	☐
Ticarcillin	☐	☐
Other:	☐	☐
If other (please specify):		
Don’t know	☐	☐

*It is not essential that the name of the specific penicillin causing the allergic reaction is given provided the assessor is confident the patient is describing a penicillin drug.

PART B: Any reason it would not be safe for the patient to undergo a drug provocation test		
Did any of the following occur during the index reaction to penicillin? (select all that apply)	**Yes**	**No**
Severe reaction needing hospital admission	☐	☐
Rash with blistering, loss of skin, bruising	☐	☐
Swelling of face or tongue at any time during course of penicillin	☐	☐
Swelling of other parts of the body	☐	☐
Difficulty breathing (including wheezing)	☐	☐
Collapse	☐	☐
Palpitations	☐	☐
Anaphylaxis	☐	☐
Urticaria or other rash which occurred within two hours of taking the first dose of penicillin	☐	☐
Did the reaction require treatment with?	☐	☐
If 'Yes' please select the treatment provided (select all that apply) Adrenaline ☐ Steroids (oral or intravenous) ☐ Antihistamine ☐		
Does the patient have severe respiratory disease or unstable coronary artery disease, or are they acutely unwell?**	☐	☐
Is the patient taking any antihistamines which cannot be stopped for three days prior to the challenge test?	☐	☐
Is the patient taking omalizumab?	☐	☐

****Definitions:**

- Severe respiratory disease includes COPD, asthma or bronchiectasis requiring a course of steroids in the past three months.
- Unstable coronary artery disease requiring daily use of sublingual or spray Glyceryle trinitate (GTN spray)

PART C: What symptoms have occurred		
Select all that apply	**Yes**	**No**
Rash (no blistering, non-itchy)	☐	☐
Childhood rash (no further details known)	☐	☐
Dizziness or headache as only symptom	☐	☐
Nausea	☐	☐
Vomiting	☐	☐
Abdominal discomfort or diarrhoea	☐	☐
Thrush	☐	☐
Patient has never taken penicillin but avoids due to family history of penicillin allergy	☐	☐
Patient has subsequently taken the same penicillin that caused the index reaction, without any adverse effects (or if index penicillin not known, has taken amoxicillin or co-amoxiclav)	☐	☐

PART D: Safe for drug provocation test?		
Select single most appropriate	**Yes**	**No**
A. Patient can have a drug provocation test. Patient had no high-risk features identified in PART B and at least one low-risk feature was identified in PART C.	☐	☐
B. Patient cannot have a drug provocation test. At least one high-risk feature was identified in PART B and/or no low-risk features were identified in PART C.	☐	☐
C. Uncertain. Patient should not have a drug provocation test without further discussion with an allergy specialist doctors. One or more features in Parts B or C could not be assessed with confidence.	☐	☐
If option C is selected please give details including any personal concern about the allocation:		

8.8 Appendix 8: Inter-rater agreement (allergist vs non-allergist) for individual questions within PASSPORT risk stratification tool

Risk stratification question	% Agreement between allergist and non-allergist raters
Is the patient taking omalizumab	98%
Is the patient taking antihistamines which cannot be stopped for three days prior to a challenge test	95%
Family history of penicillin allergy	95%
Collapse	94%
Anaphylaxis	92%
Swelling of other parts of the body	90%
Difficulty breathing (including wheezing)	90%
Palpitations	89%
Does the patient have severe respiratory disease or unstable coronary artery disease, or are they acutely unwell	88%
Patient has taken the same penicillin since without any problems (or if index penicillin not known, had taken amoxicillin or co-amoxiclav)	88%
Severe reaction needing hospital admission	86%
Abdominal discomfort or diarrhoea	86%
Thrush	86%
Dizziness or headache as the only symptom	85%
What was the name of the penicillin that caused the allergic reaction	83%
Rash with blistering, loss of skin or bruising	83%

Childhood rash (no further details known)	83%
Swelling of face or tongue at any time during course of penicillin	82%
Nausea	82%
Vomiting	80%
Did the reaction require treatment with adrenaline and/or steroids and/or antihistamines	71%
Rash (non-blistering, non-itchy) which did not occur within the first two hours of taking the first dose	64%
Urticaria or other rash which occurred within 2 hours of taking the first dose of penicillin	62%

8.9 Appendix 10: Topic guide for healthcare professional interviews/focus groups in PASSPORT Process Evaluation

Interview topic guide for allergists and non-allergists

1. Overall, how easy did you find the risk stratification tool to use?
2. Can you describe any positive or negative aspects to using the tool?
3. Can you tell me what you think about each of the questions on the risk stratification tool in turn (clarity of question, likelihood of clear response from patient, whether it feels relevant, whether the reason for asking is clear to the person using the tool). (This question will focus heavily on the key areas of difference seen in the study)
4. Were there any specific questions/parts of the tool which didn't make sense to you?
5. Were there any questions you found it particularly difficult to get a clear answer to from the patient?
6. How easy to you find it to gauge whether co-morbidity would be severe enough to preclude challenge testing?
7. When asking the questions, did you imagine yourself being the person to actually give the subsequent challenge test?
8. If you were using this perioperatively and proceeding to a challenge test in low-risk patients, would this change your approach to risk stratification? If so, how?
9. On analysing the data, we found that the tool gave an incorrect risk stratification in 39% of patients. The key questions implicated in these differences were around diagnosis of rash, significance of uneventful re-exposure to the penicillin, and the importance of co-morbidities. Does that align with your experience of using the tool?
10. How do you think the performance of the tool could be improved? (eg further detail on the 'tricky' questions, or better training for users?)
11. Is there any specific training you think users of this tool might need in order to improve its performance and reliability?
12. Is there anything which would increase your confidence in using the tool?

8.10 Topic guide for qualitative study in patients referred to allergy clinic with suspected perioperative allergic reactions

Note: This interview schedule was not fixed and questions could be tailored according to the specific answers of each interviewee. The interview schedule below was a general topic guide.

Welcome and Introduction.
Ask if any questions. Obtain informed consent

Re-cap of Research and Plan for Interview
Brief re-cap on the aims and purpose of the interview and explain what will happen.

The following questions need not be covered in this particular order but rather the interview should flow as freely and naturally as possible. The interviewer will prompt as appropriate with phrases such as 'can you tell me a little more about that', 'can you give me an example of that', 'how did/do you feel about that'.

It may be upsetting for the patient to talk about some parts of their experience. It is important to give them time to talk about this. Modify the questions on the basis of what they say about their overall experience.

<u>Interview guide: PRE-CLINIC INTERVIEW</u>

Introduction

- Confirm consent for recording
- Explain role of researcher
- Reiterate that this is one of two interviews (the second to take place 1-2 weeks after the clinic visit) and the reason for the second interview.

Starting the conversation

- Can you tell me what happened before or during your operation that meant you were referred to the allergy clinic?

Understanding of the initial reaction

- Can you tell me what you remember about going off to sleep?
- Can you remember how you felt when you woke up?
- How do you feel about what happened to you?

- *Further question: do you have any flashbacks or memories that keep coming back to you about what happened? If so, could you describe them? Are these upsetting or disturbing?*

- Do you remember if any information was given to you about what had happened to you? If so, did the information you were given make sense to you at the time and since?
  - *Further question if yes: what sort of information were you given and did you find this helpful?*
- Was the information you were given clear and useful?
- Have your feelings about what happened changed in any way since you came out of hospital?
  - *Further question if yes: how has your interpretation of/feelings around what happened changed and why?*
- What is your general health like at the moment?
- Do you feel this has changed since you the event happened?
- Have you needed any healthcare since this problem happened?
  - *Further question if yes: have you avoided any healthcare and if so why? Have your GP or other healthcare practitioners avoided doing something because they are waiting for the results from the allergy clinic? What impact has all of this this had on yo,u if so?*
- Are you concerned about what happened to you?
  - *Further question if yes: what is your main concern? Can you explain a bit about this?*

Understanding the purpose of the clinic

- Can you explain in your own words what you think will happen when you go to the allergy clinic?
- What are you hoping to get out of coming to the clinic?
- Are you worried about any aspect of the clinic visit and/or the testing?
- Is there any information you would find helpful before coming to the clinic?

- *Further question if yes: would you find it useful to have written or digital information? Videos explaining what will happen?*

- What sorts of tests are you expecting to be done when you come to clinic?
- Do you already know anything about allergy testing?
  - *Further question if they have experience of allergy testing: what testing have you/someone you know, previously experienced?*
- Do you anticipate that the testing you undergo at clinic will give you an answer about what happened during your operation?
  - *Further question: if no, can you explain why you are not confident you will get answer/if yes, can you explain why you are confident you will have an answer?*
- Is your expectation that all the testing you need will be carried out during the clinic, or that you might need to come back for more testing?
- Do you think the clinic will be useful, or is this just something you have been told you have to come to?

Ending the conversation

- Is there anything else you would like to talk about that hasn't been covered? Or anything else you think that might be of interest which we haven't talked about?

Thank the participant for taking part.

<u>Interview guide: POST-CLINIC INTERVIEW</u>

Starting the conversation

- Confirm consent for recording
- Confirm the date of the clinic which the patient attended

Experience at the clinic

- Can you remember who was in the clinic you attended, in terms of the specialty of the doctors and their role in the clinic?
- Can you describe what was done at the clinic, in your own words?
- How did you find the experience of undergoing allergy testing?
    - *Further question: if positive or negative experience, explore why/how*
- Can you describe in your own words the purpose of each test you had done? How well did you feel this was explained to you by the doctors or nurses in clinic?
- How did you feel when you were discussing the event with the doctors in clinic?
- Looking back, is there any information it would have been useful to have, prior to coming to the clinic appointment?

Understanding of the clinic output

- Can you tell me, in your own words, what the doctors in the clinic said had happened to you during your operation?
- Did you feel the explanation they gave was helpful to you and made sense?
    - *Further question if no: which bit of what was said did not make sense to you? Can you explain why not?*
- Was the explanation you were given what you were expecting to hear, or did it differ in some way?
- Did you feel you were given a complete answer about what happened, or are there still question marks in your mind about what happened?
    - *Further question for patients with outstanding issues and awaiting further investigations:*
- What investigations are you still waiting for?
- How do you feel about not yet having a diagnosis for what happened to you?
- How does this affect your day to day life?
- Are you waiting for another operation that cannot do ahead until these investigations are completed? And if so, how do you feel about this?

Understanding of the impact on future healthcare

- What impact do you think the diagnosis you have been given will have on you in the future?
- Specifically, do you think this will have any impact on any future surgery you might need?
- Are you worried about needing surgery in the future and the safety of this?
- Do you think the diagnosis you have been given is generally a positive, or negative thing for you?
- Do you think your diagnosis will have an impact on anyone else in the family?
- What steps do you plan to take to tell your GP and other doctors about the allergy diagnosis?
    - *Further question if this was a confirmed allergy: do you plan to wear a medic-alert bracelet or similar? If not, what is the reason for this?*

Ending the conversation

- Is there anything else you would like to talk about that hasn't been covered? Or anything else you think that might be of interest which we haven't talked about?

Thank the patient for taking part.

8.11 Ethical approvals

8.11.1 SAPPHIRE study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Tom Abbott
NIHR Clinical Lecturer in Anaesthesia & Perioperative Medicine
Barts Health NHS Trust
Adult Critical Care Unit
Royal London Hospital
London
E1 1FR

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

07 February 2022

Dear Dr Abbott

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Safe Antimicrobial ProPhylaxis for surgery study**
IRAS project ID:	**282161**
REC reference:	**22/YH/0040**
Sponsor	**Barts Heath NHS Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **282161**. Please quote this on all correspondence.

Yours sincerely,

Hayley Henderson
Approvals Manager

Email: approvals@hra.nhs.uk

Copy to: *Dr Mays Jawad, Barts Health NHS Trust*

8.11.2 SPACE study

Professor Mamidipudi Thirumala Krishna
Consultant Allergist and Immunologist and Honorary Professor in Allergy, Clinical Immunology and Global Health
University Hospitals Birmingham NHS Foundation Trust
Bordesley Green East
Birmingham
West Midlands

Email: approvals@hra.nhs.uk

23 July 2021

Dear Professor Thirumala Krishna

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**A Multicentre Study to Investigate a Protocol-Driven Multidisciplinary Service Model to Tackle 'Spurious Penicillin Allergy' in Secondary Care (SPACE study)**
IRAS project ID:	**293544**
REC reference:	**21/PR/0814**
Sponsor	**R&D Department**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **293544**. Please quote this on all correspondence.

Yours sincerely,
Juliana Araujo

Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Mr Clark Crawford, Head of Research Governance*

8.11.3 PASSPORT study

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **313986**. Please quote this on all correspondence.

Yours sincerely,
Deanna Herron

Approvals Specialist

Email: approvals@hra.nhs.uk
Copy to: *Ms Sarah Hall*

8.11.4 Qualitative study of patients who experience suspected perioperative allergic reactions

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Louise Savic
Consultant Anaesthetist and NIHR Doctoral Fellow
Leeds Teaching Hospitals NHS Trust
St James' University Hospital
Beckett Street
Leeds
LS9 7TF

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

13 April 2023

Dear Dr Savic

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Understanding the views, perspectives and behaviours of patients with suspected perioperative allergy: a qualitative study of patients referred to and attending the perioperative allergy clinic**
IRAS project ID:	**324837**
Protocol number:	**GS23/156788**
REC reference:	**23/NE/0058**
Sponsor	**Leeds Teaching Hospitals NHS Trust Research and Innovation Centre**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **324837**. Please quote this on all correspondence.

Yours sincerely,
Libby Williamson
Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Sarah Hall*

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