National Clinical Guideline Centre

NICE clinical guideline 183

Drug allergy

Diagnosis and management of drug allergy in adults, children and young people

Clinical guideline 183

Methods, evidence and recommendations

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Update information

November 2018: After a surveillance review, a link to other NICE guidance was updated as the original guidance had been replaced.
These changes can be seen in the short version of the guideline at:
https://www.nice.org.uk/guidance/cg183

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1 Introduction

All drugs have the potential to cause side effects, also known as 'adverse drug reactions', but not all of these are allergic in nature. Other reactions are idiosyncratic, pseudo-allergic or caused by drug intolerance. The British Society for Allergy and Clinical Immunology (BSACI) defines drug allergy as an adverse drug reaction with an established immunological mechanism. The mechanism at presentation may not be apparent from the clinical history and it cannot always be established whether a drug reaction is allergic or non-allergic without investigation. Therefore, this guideline has defined drug allergy as any reaction caused by a drug with clinical features compatible with an immunological mechanism.

Hospital Episode Statistics from 1996 to 2000 reported that drug allergies and adverse drug reactions accounted for approximately 62,000 hospital admissions in England each year. There is also evidence that these reactions are increasing: between 1998 and 2005 serious adverse drug reactions rose 2.6-fold.[116] Up to 15% of inpatients have their hospital stay prolonged as a result of an adverse drug reaction.

About half a million people admitted to NHS hospitals each year have a diagnostic 'label' of drug allergy, with the most common being penicillin allergy. About 10% of the general population claim to have a penicillin allergy;[79] this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic.[79] Therefore, penicillin allergy can potentially be excluded in 9% of the population.[36,61]

Studies have shown that those with a label of penicillin allergy are more likely to be treated with broad-spectrum antibiotics, such as quinolones, vancomycin, and third-generation cephalosporins (Lee, 2000)[96]. Use of broad-spectrum antibiotics is associated with an increased rate of clinical complications, such as antibiotic resistance and *Clostridium difficile* leading to increased hospital stay (Macy,2014)[102]. Patients in intensive care who developed vancomycin-resistant enterococcus (VRE) were 5 times more likely to have been treated with vancomycin and third generation cephalosporins during the previous month (Martinez, 2003)[108]. Therefore, an unsubstantiated label of penicillin allergy may lead to the inappropriate use of broad spectrum, non-penicillin antibiotics leading to antibiotic resistance and in some cases sub-optimal therapy.

Allergic reactions to non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, naproxen and aspirin are common.[61,78] In particular, 5–10% of people with asthma are affected. About one-third of people with chronic urticaria have severe reactions to NSAIDs, involving angioedema and anaphylaxis after administration of NSAIDs.[34,117]

Anaphylaxis-type reactions occur in approximately 1 in 1000 of the general population. Anaphylaxis during general anaesthesia occurs in between 1 in 10,000–20,000 anaesthetics.[46,47] These patients may be denied general anaesthesia in the future unless a safe combination of drugs can be identified.[115]

Major issues identified by this guideline include poor clinical documentation of drug allergy and a lack of patient information. Computerised primary care record systems are often unable to distinguish between intolerance and drug allergy and this can lead to a false label of drug allergy, particularly if the person's reaction took place many years previously and details about their reaction have been lost. Furthermore, there is no routine system in place for people to keep a record of their own drug allergies. This can lead to confusion over which drugs can be taken safely and can result in people inadvertently taking a drug they are allergic to, particularly when buying over-the-counter preparations from a pharmacy.

Analysis of patient safety incidents reported to the National Reporting and Learning System between 2005 and 2013 identified 18,079 incidents involving drug allergy. These included 6 deaths, 19 'severe

harms', 4980 'other harms' and 13,071 'near-misses'. The majority of these incidents involved a drug that was prescribed, dispensed or administered to a patient with a previously known allergy to that drug or drug class.

Diagnosing drug allergy can be challenging and there is considerable variation both in how drug allergy is managed and in geographical access to treatment. This can lead to under-diagnosis, misdiagnosis and self-diagnosis. This variation may be caused by insufficient awareness of available services or by a lack of local provision of drug allergy centres. Some people are never offered referral to specialist services and instead stay in primary care while others have their drug allergy managed in other disciplines. Therefore, only a small proportion of people are treated in specialist allergy centres.

In view of the variation in provision of care for people with drug allergy, the scope of this guideline identified a need for guidance to improve clinical management for people affected by drug allergy. Although NICE guidance would normally refer to the term 'medicine' rather than 'drug', in this instance the term 'drug allergy' has been adopted as this is the term widely recognised and in common usage, and reflects the focus on drug treatments rather than other preparations.

This guideline has been developed for use by healthcare professionals at all levels of healthcare and offers best practice advice on the diagnosis, documentation and communication of drug allergy in adults, children and young people.

2 Development of the guideline

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- the 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

Drug allergy: the diagnosis and management of drug allergy in adults, children and young people.

2.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Dr Shuaib Nasser in accordance with guidance from NICE.

The group met every 5 to 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

(a) What this guideline covers

This guideline covers the diagnosis and management of drug allergies. For further details please refer to the scope in Appendix A and the review questions in Section 3.1.

(a) What this guideline does not cover

This guideline does not cover other allergies (for example food allergies), treatment of the acute phase including anaphylaxis, investigation of allergies to individual drugs or in specific populations (unless specified in the scope), or treatment of non-allergic adverse drug reactions.

(b) Relationships between the guideline and other NICE guidance

This guideline is related to the following NICE guidance:

1. Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
2. Medicines adherence. NICE clinical guideline 76 (2009).
3. Technical patient safety solutions for medicines reconciliation on admission of adults to hospital. NICE patient safety solutions guidance 1 (2007).
4. Managing medicines in care homes. NICE social care guideline 1 (2014)
5. Anaphylaxis. NICE clinical guideline 134 (2011).

The following related NICE guidance is currently under development, details are available from the NICE website:

1. Medicines optimisation. NICE clinical guideline. Publication expected March 2015.
2. Antimicrobial stewardship. NICE clinical guideline. Publication expected March 2015.

3 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[125]

3.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews; in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy; and using population, presence or absence of factors under investigation (for example prognostic factors) and outcomes for prognostic reviews. The experience of information provision for people with suspected or confirmed drug allergies was reviewed using qualitative information to capture preferences and perceptions (including factors which improve or act as a barrier to optimal care).

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 11 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
Assessment	Review of commonalities across drug allergies assessment scores and algorithms	What is the clinical and cost effectiveness of clinical probability scores or algorithms in identifying or excluding drug allergies?	• Commonalities and differences across algorithms and probability scores • Features that assess likelihood of people having drug allergies
Measuring serum tryptase after suspected anaphylaxis	Diagnostic accuracy review	What is the clinical and cost effectiveness of serum tryptase testing compared with reference standard tests for the diagnosis of an anaphylactic reaction due to suspected drug allergy?	• Test accuracy measures: • Pre-test probability • Sensitivity • Specificity • Positive predictive value • Negative predictive value • Number of cases missed
Measuring serum specific immunologulin E (IgE)	Diagnostic accuracy review	What is the clinical and cost effectiveness of serum specific IgE testing compared with reference standard tests in the diagnosis of drug allergy for the following drugs? amoxicillin	• Test accuracy measures: • Pre-test probability • Sensitivity • Specificity

Chapter	Type of review	Review questions	Outcomes
		ampicillin cefaclor chlorhexidine morphine penicillin G penicillin V suxamethonium.	• Positive predictive value • Negative predictive value • Number of cases missed • Number of cases mislabelled
Documenting and sharing information with other healthcare professionals	Intervention review	What are the most clinically and cost effective documentation strategies for communicating drug allergy information across all NHS services to prevent patients from receiving drugs to which they are allergic?	• Medication errors (inappropriate prescription or administration of drugs) • Number of repeat drug allergic reactions (including patient-reported episodes) • Inappropriate avoidance of drugs • Health-related quality of life
Providing information and support to patients	Qualitative review	What information and support should individuals with suspected drug allergy or their parents and carers receive? What information and support should individuals who have had specialist investigations or their parents and carers receive?	• Patient experiences • Preferences or perceptions, including factors which improve or act as barrier to optimal care • Clinical and quality of life outcomes related to diagnosis and management of drug allergy
Non-specialist management	Prognostic review	In patients who have had allergic reactions to NSAIDs what are the factors that indicate whether they can or cannot tolerate selective COX-2 inhibitors?	• Incidence and severity of reaction to selective COX-2 inhibitors, such as asthma, angioedema or urticaria • Incidence of other adverse events
Referral to specialist drug allergy services	Intervention review	What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected drug allergy to beta-lactam antibiotics? What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to NSAIDs? What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to local	• Mortality • Number of repeat drug allergic reactions (including patient reported episodes) • Length of hospital stay • Inappropriate avoidance of drugs. • Health-related quality of life

Chapter	Type of review	Review questions	Outcomes
		anaesthetics? What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected anaphylaxis due to drug allergy during general anaesthesia?(a)	

(a) This question was phrased differently to the other 3 review questions regarding referral – it relates to people with suspected anaphylaxis rather than people with suspected drug allergy – since it refers to an immediate severe reaction during general anaesthesia.

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the NICE guidelines manual 2012.[125] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. In additional Cinahl was used for the information and support review. All searches were updated on 10 January 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (http://www.g-i-n.net/)
- National Guideline Clearing House (http://www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (http://www.nice.org.uk/)
- National Institutes of Health Consensus Development Program (http://consensus.nih.gov/)
- NHS Evidence Search (http://www.evidence.nhs.uk/)
- British Society for Allergy & Clinical Immunology (BSACI) (http://www.bsaci.org/)
- American Academy of Allergy, Asthma & Immunology (AAAAI) (http://www.aaaai.org/home.aspx).

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to drug allergy in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with

no date restrictions. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2011, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. For databases, where it was possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. All searches were updated on 15 January 2014. No papers published after this date were considered.

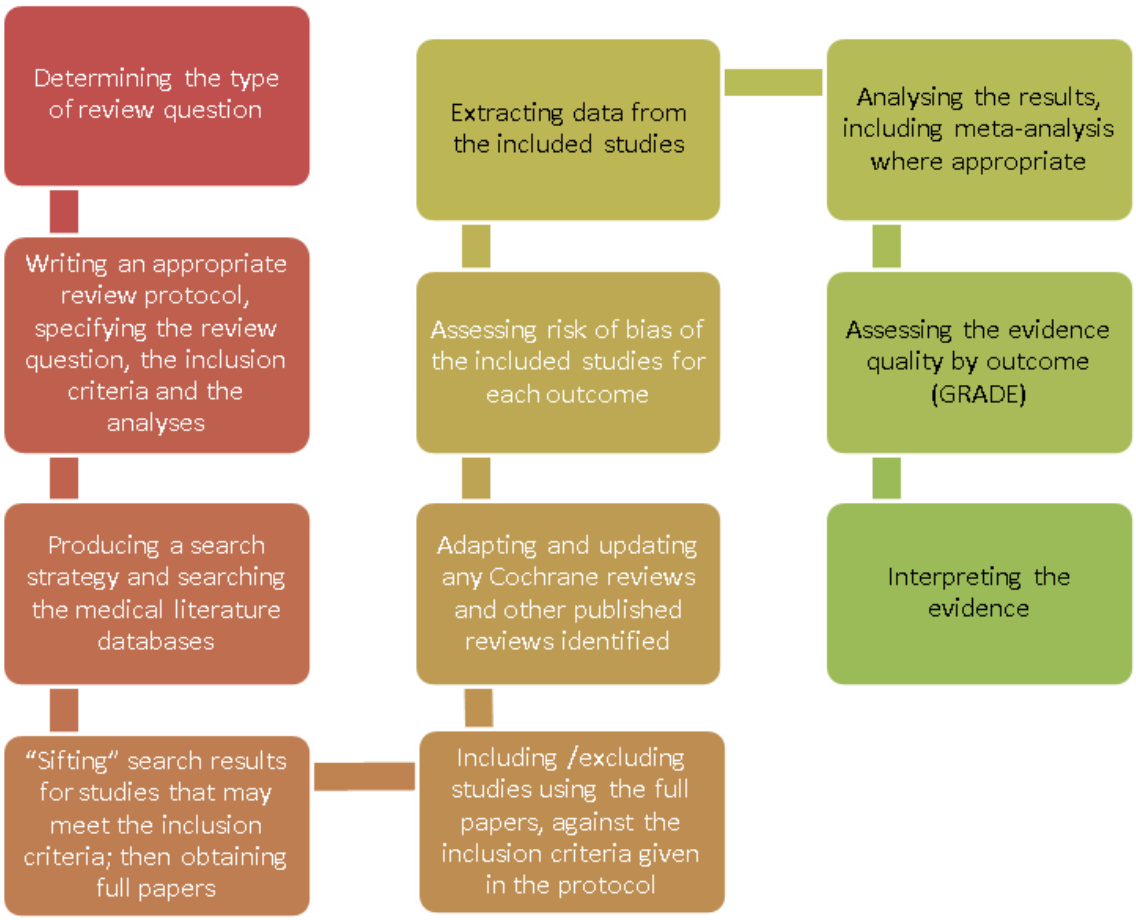
3.3 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual (2012).[125] For diagnostic questions, the QUADAS-2 checklist[163,171] was followed (see Appendix F of The guidelines manual (2012)).
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
    - Observational studies: data were presented as a range of values in GRADE profiles.
    - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors.
    - Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value). Coupled values of sensitivity and specificity were summarised in paired (sensitivity and specificity side by side) forest plots to allow visual comparison between different index tests and to investigate heterogeneity more effectively (given data were reported at the same thresholds).
    - Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

  A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Figure 1: Step-by-step process of review of evidence in the guideline



3.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The guideline population was defined to be people with suspected or confirmed drug allergies. For some review questions, the review population was defined by the drug or drug class the person was allergic to (for example beta-lactam antibiotics, non-steroidal anti-inflammatories, local anaesthetics or general anaesthetics in review questions 8 to 11).

In the diagnostic chapter serum IgE testing was reviewed for a list of drugs that was prioritised by the GDG: amoxicillin, ampicillin, cefaclor, chlorhexidine, morphine, penicillin G, penicillin V, and suxamethonium.

The diagnostic serum tryptase review was restricted to patients with signs and symptoms of anaphylaxis.

Even though the prognostic review (to examine if there were certain characteristics of people with an allergy to NSAIDs who could take selective COX-2 inhibitors) had identified specific characteristics as prognostic factors, studies that were not designed to directly address these factors were not excluded. Studies that investigated the safety of taking selective COX-2 inhibitors for people with an allergy to NSAIDs more generally were included as indirect evidence. These studies were then divided by the study population (people with asthma or people with cutaneous reactions) to address the prognostic aspect of the question. For details of the approach to this review please refer to Chapter 11.

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question, in which case the authors of the selected abstracts were contacted for further information. None of the reviews in this guideline included conference abstracts as part of the evidence.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C.

3.3.2 Methods of combining clinical studies

3.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as number of patients being treated with alternative beta-lactam antibiotics, or number of patients with medication errors.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes (such as prescription errors) were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out predefined subgroup analyses for type of drug allergy and age group (children or adults).

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the

individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

3.3.2.2 Data synthesis for prognostic factor reviews

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors were extracted from the papers when reported. For the purpose of the review question on tolerance of selective COX-2 inhibitors, factors that indicated whether the drug was safe to prescribe regardless of prognostic factors were also noted, such as the type of allergic reaction and the rate of severe reactions in response to the selective COX-2 inhibitor.

3.3.2.3 Data synthesis for diagnostic test accuracy reviews

Data and outcomes

For the reviews of diagnostic test accuracy, a positive result on the index test was found if the patient had values of the measured quantity above a threshold value, and different thresholds could be used. Diagnostic test accuracy measures used in the analysis were: sensitivity, specificity, positive and negative predictive value. The threshold of a diagnostic test is defined as the value at which the test can best differentiate between those with and without the target condition (for instance different thresholds were used in the serum tryptase review) and, in practice, it varies amongst studies. For this guideline, sensitivity and specificity were considered equally important. A high sensitivity (true positives) of a test can pick up the majority of the correct cases with drug allergy; conversely, a high specificity (true negatives) can correctly exclude people without drug allergy.

Data synthesis

Coupled forest plots of sensitivity and specificity with their 95% CIs across studies (at various thresholds) were produced for each test, using RevMan5. In order to do this, 2×2 tables (the number of true positives, false positives, true negatives and false negatives) were directly taken from the study if given, or else were derived from raw data or calculated from the set of test accuracy statistics.

Heterogeneity or inconsistency amongst studies was visually inspected in the forest plots where appropriate (only when there were similar thresholds). A diagnostic meta-analysis was not carried out because studies were not homogenous enough to assume a single underlying level of sensitivity and specificity (due to differences in population, type of index test or reference standard).

3.3.2.4 Data synthesis for qualitative study review

Where possible a meta-synthesis was conducted to combine qualitative study results. The main aim of the synthesis of qualitative data was a description of the main topics that may influence the experience of care of the person with suspected or confirmed drug allergy or their parents or carers, rather than build new theories or reconceptualise the topic under review. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had identified this theme. A frequently identified theme may indicate an important issue for the review, but frequency of theme is not the only indicator of importance. Study type and population in qualitative research can differ widely meaning that themes that may only be identified by one or a few studies can provide important new

information. Therefore for the purpose of the qualitative review in this guideline the categorisation of themes was exhaustive, that is all themes were accounted for in the synthesis. The GDG could then draw conclusions on the relative merits of each of the themes and how they may help in forming recommendations.

3.3.2.5 Data synthesis for the algorithm and probability score review

The aim of this review was to summarise evidence on issues that clinicians need to consider when assessing a person with a suspected drug allergy and the signs and symptoms that the person would present with. Assessments should be suitable for the primary care setting. It was decided that this topic would be best addressed with a review of already published assessment methods (that is, algorithms and probability scores) because of the multitude of individual features that may indicate a potential drug allergy. After a top-level search on this topic a published systematic review was identified (Agbabiaka 2008[3]). This review was edited (studies restricted to adverse drug events without drug allergies were excluded) and updated. For a full description of this specific data synthesis approach please see Chapter 6.

3.3.2.6 Data synthesis for the documentation review

The aim of this review was to summarise evidence on the effectiveness of documentation strategies in preventing people with suspected or confirmed allergies receiving the drug they are allergic to. Study types considered for this review were randomised trials, and systematic reviews. Prospective and retrospective cohort studies, before and after studies, case series, surveys and qualitative studies were also considered, with the caveat that if a lot of evidence was identified for a particular documentation intervention then only the higher-level evidence be included in the review.

Due to the multitude of populations, study designs, interventions and reported outcomes an exception was made to the usual effectiveness reviews described above. The following approach was used:

- Evidence was classified according to the broad documentation category (for example, computerised systems or structured charts).
- Features of different documentation categories were then extracted.
- Outcomes (such as prescribing errors or alerts that were overwritten) were summarised and where possible related to the features of the documentation strategy.
- Study quality was assessed individually and then by the majority of evidence for a particular intervention and outcome.
- Overall quality was then assessed by documentation category.

Further details of this approach are described in Chapter 9.

3.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. For example in the questions on referral to specialist drug allergy services it was decided to include non-randomised trials since randomisation might not always be possible or appropriate.

For the diagnostic reviews and the algorithm and probability score review, cross-sectional and retrospective studies were included. For prognostic reviews, prospective and retrospective cohort studies were included.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

3.3.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 3.3.5 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy studies.

Table 2: Description of the elements in GRADE used to assess the quality of intervention and diagnostic studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity, as assessed by the I-squared or Chi-squared statistic in intervention reviews or visual inspection of paired sensitivity and specificity forest plots in diagnostic reviews (that is, when point estimates in sensitivity and specificity vary widely across studies).
Indirectness	Indirectness refers to differences in study population, intervention or diagnostic index test, comparator or diagnostic comparator test and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Intervention reviews: Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold but ranges from appreciable benefit to no effect or possible harm. Diagnostic reviews: Results are considered to be imprecise if the confidence interval around either the pooled sensitivity or specificity (or if not pooled the confidence interval of the median) ranges between 10–20% (serious) or above 20% (very serious).
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying

Quality element	Description
	beneficial or harmful effect due to the selective publication of studies. This aspect was not assessed in the diagnostic test accuracy reviews.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

3. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
4. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
5. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
6. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the following Sections 3.3.6 to 3.3.9.

3.3.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 5.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules Use of unvalidated patient-reported outcomes Recruitment bias in cluster-randomised trials

3.3.6.1 Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist was used (see Appendix F of The guidelines manual (2012)[125]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 2):

- patient selection
- index test
- reference standard
- flow and timing.

Figure 2: Summary of QUADAS-2 checklist

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting):	Describe the index test and how it was conducted and interpreted:	Describe the reference standard and how it was conducted and interpreted:	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: QUADAS-2 website, University of Bristol[163]

Optional domain, multiple test accuracy is applicable when a single study examined more than 1 diagnostic test (head-to-head comparison between 2 or more index tests reported within the same study). This optional domain contains 3 questions relating to risk of bias:

- Did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients?
- Were index tests conducted within a short time interval?
- Are index test results unaffected when undertaken together on the same patient?

3.3.6.2 Prognostic studies

For prognostic studies, quality was assessed using the checklist for prognostic studies (Appendix I in The guidelines manual (2012)[125]). The quality rating (Low, High, Unclear) was derived by assessing the risk of bias across 6 domains: selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed for each outcome. A summary table on the quality of prognostic studies is presented at the beginning of each review to summarise the risk of bias across the 5 domains. More details about the quality assessment for prognostic studies are shown below:

- The study sample represents the population of interest with regard to key characteristics
- Missing data are unrelated to key characteristics, sufficient to limit potential bias – reasons for missing data are adequately described.
- The prognostic factor of interest is adequately measured in study participants.
- The outcome of interest is adequately measured in study participants.
- Important potential confounders are accounted for appropriately.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of valid results.

Many of the studies in the prognostic review were safety studies, that is, they did not directly investigate particular factor and in these cases the checklist for non-randomised studies was used.

3.3.6.3 Qualitative studies

For qualitative studies, quality was assessed using the checklist for qualitative studies (Appendix I in The guidelines manual (2012)[125]). The quality rating (Low, High, Unclear) was derived by assessing the risk of bias across 6 domains:

- theoretical approach
- study design
- data collection
- validity
- analysis
- ethics.

3.3.6.4 Algorithm and probability score studies

For these studies none of the checklists adequately addressed the specific quality criteria deemed important by the GDG. A checklist was therefore designed for these studies to assess risk of bias across 9 criteria:

These criteria were based on factors that were considered in the narrative assessment of the algorithms within the systematic review[3] included in the chapter (see 6.2.1):

1. Design of the tool:

How the tool was designed in a systematic way (that is, using a statistical method or by way of literature review)

2. Factors that are considered:

Whether or not a sufficient number of features were considered

3. Applicability to clinical practice (primary care):

The aim of the review was to find an assessment that could be carried out in general practice and was therefore applicable to current practice.

4. Definition of condition:

Whether the tool was based on a clear definition of the condition for which it was going to be used.

5. Number of evaluators or assessors:

Whether in the design of the tool separate independent evaluators were used and their assessments were analysed for consistency.

6. Prior probabilities:

Whether the group that was assessed was generalisable to the general population of people with drug allergies or whether only high risk participants were assessed by the tool.

7. Validation in independent studies:

Whether this test has been further used as a reference standard in other test comparisons

8. Confounders or alternative conditions:

Whether plausible alternative conditions or factors that may affect the result of the algorithm were considered

9. Ease of interpretation:

Whether the test could be easily and quickly scored and also whether the result or 'score' could be easily interpreted in primary care.

This quality checklist was used by 2 reviewers independently and differences in assessments were discussed and agreed.

3.3.7 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.3.8 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

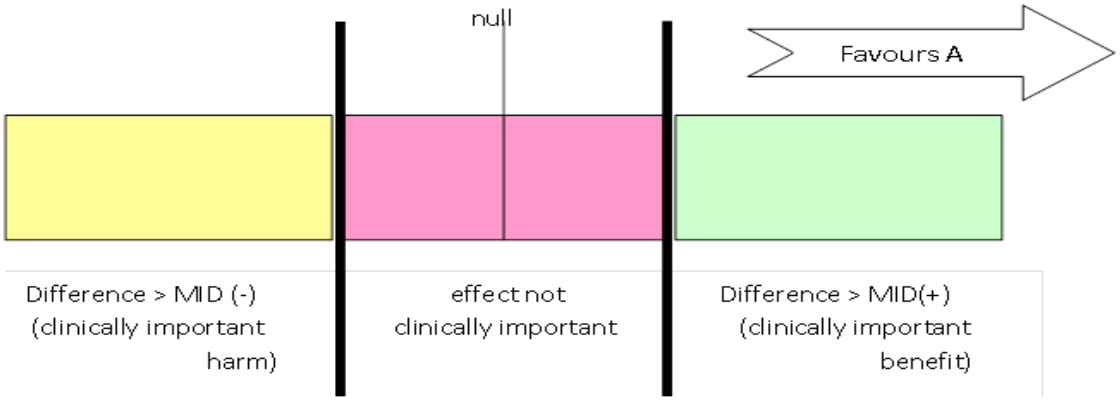
3.3.9 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 3 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 3: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community. Finally, the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews.

3.3.10 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[125] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economists:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual (2012).[125]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix I).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

3.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded. No economic evaluations were identified that related to a review question and satisfied these criteria. Therefore, no economic evaluations were included in this guideline.

Remaining studies would have been prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis had been available, then other less relevant studies may not have been included. However, no exclusions occurred on this basis in this guideline, as all studies had already been excluded on the grounds of not being a full economic evaluation or not relating to any of the review questions, and so no economic evaluations were listed in the excluded economic studies appendix (Appendix L).When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economists in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified referral to specialist drug allergy services or alternative management strategies within primary care for patients who are not referred as the highest priority area for original economic analysis. The GDG believed that economic modelling in this area would be informative if feasible, but concluded that modelling was unfortunately not feasible as information was not available on the relative effectiveness of referral or non-specialist management on outcomes such as the number of future allergic reactions or the number of occasions alternative drugs are used. This was due both to the fact that as specialist management is outside the scope of this guideline the referral pathway is undefined, and to the lack of applicable published economic research on the areas that are within the scope. Therefore any model would necessarily have to be built largely upon estimates and assumptions. In particular, sufficient data were not available to allow modelling of different subgroups, which would be necessary to identify which individuals should or should not be referred to specialist drug allergy services.

Instead of conducting a full economic evaluation, 4 cost-effectiveness scenarios were constructed for the case of suspected allergy to beta-lactam antibiotics. These calculated the potential costs of both referral to specialist drug allergy services and of non-specialist management for multiple frequencies of future need for antibiotics. They presented the magnitude of difference in quality of life (measured in quality-adjusted life years [QALYs] or life days [QALDs]) which referral would need to be expected to yield for it to be cost effective compared to non-specialist management. The GDG used these scenarios to inform their recommendations regarding which people should and should not be referred to specialist drug allergy services.

The following general principles were adhered to in developing the cost-effectiveness scenarios:

- Methods were consistent with the NICE reference case.[126]
- The GDG was involved in the design of the scenarios, selection of conditions and drugs examined and interpretation of the results.
- Costs were based on routine NHS data sources.
- Inputs and assumptions were reported fully and transparently, and their limitations were discussed.

Full methods for the cost-effectiveness scenarios for referral to specialist drug allergy services are described in Chapter 12.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[123] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained,

the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[123]

When QALYs or life years gained are not used in an analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summaries of clinical and economic evidence and quality (as presented in Chapters 6–12).
- Forest plots (Appendix J).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 3.5.1 below).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in The guidelines manual (2012)[125]).

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

3.5.5 Funding

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4 Algorithm

SUSPECTED DRUG ALLERGY

ASSESSMENT

SIGNS AND ALLERGIC PATTERNS OF SUSPECTED DRUG ALLERGY WITH TIMING OF ONSET:

When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following as a guide when deciding whether to suspect drug allergy:

Immediate, rapidly evolving reactions:

Anaphylaxis – a severe multi-system reaction characterised by:
- erythema, urticaria or angioedema **and**
- hypotension and/or bronchospasm

Urticaria or angioedema without systemic features

Exacerbation of asthma, for example with non-steroidal anti-inflammatory drugs (NSAIDs).

Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed).

Non-immediate reactions without systemic involvement
- widespread red macules or papules (exanthem-like)
- fixed drug eruption (localised inflamed skin).

Onset usually 6–10 days after first drug exposure or within 3 days of second exposure.

Non-immediate reactions with systemic involvement
- drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: widespread red macules, papules or erythrodema, fever, lymphadenopathy, liver dysfunction and eosinophilia.

Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure.

N.B. this list describes common and important presenting features of drug allergy but other presentations are also recognised.

Non-immediate reactions with systemic involvement (continued)

• Toxic epidermal necrolysis or Stevens-Johnson syndrome characterised by: painful rash and fever (often early signs), mucosal or cutaneous erosions, vesicles, blistering or epidermal detachment, red purpuric macules or erythema multiforme. *Onset usually 7–14 days after first drug exposure or within 3 days of second exposure.*

• Acute generalised exanthematous pustulosis (AGEP) characterised by: widespread pustules, fever and neutrophilia. *Onset usually 3–5 days after first drug exposure.*

• Common disorders caused, rarely, by drug allergy:
- eczema
- hepatitis
- photosensitivity
- vasculitis
- nephritis. *Time of onset variable.*

N.B. the above list describes common and important presenting features of drug allergy but other presentations are also recognised.

Be aware that the reaction is more likely to be caused by drug allergy if it occurred during or after use of the drug and:
- the drug is known to cause that type of reaction **or**
- the person has previously had a similar reaction to that drug or drug class.

Be aware that the reaction is less likely to be caused by drug allergy if:
- there is a possible non-drug cause for the person's symptoms (for example, they have had similar symptoms when not taking the drug) **or**
- the person has gastrointestinal symptoms only.

MEASURING SERUM TRYPTASE AFTER SUSPECTED ANAPHYLAXIS

After a suspected drug-related anaphylactic reaction, take 2 blood samples for mast cell tryptase in line with recommendations in Anaphylaxis (NICE clinical guideline 134).

Record the exact timing of both blood samples taken for mast cell tryptase: in the person's medical records **and** on the pathology request form.

Ensure that tryptase sampling tubes are included in emergency anaphylaxis kits.

MEASURING SERUM SPECIFIC IMMUNOGLOBULIN E

Do not use blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy in a non-specialist setting.

NON-SPECIALIST MANAGEMENT

GENERAL MANAGEMENT

If drug allergy is suspected:
- consider stopping the drug suspected to have caused the allergic reaction and advising the person to avoid that drug in future
- treat the symptoms of the acute reaction if needed; send people with severe reactions to hospital
- document details of the suspected drug allergy in the person's medical records (see documenting and sharing information below)
- provide the person with information (see providing information and support to patients below).

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (INCLUDING SELECTIVE CYCLOOXYGENASE 2 INHIBITORS)

Explain to people with a suspected allergy to a non-selective non-steroidal anti-inflammatory drug (NSAID) (and their family members or carers as appropriate) that in future they need to avoid all non-selective NSAIDs, including over-the-counter preparations.

For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:
- discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy)
- consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.

Do not offer a selective COX-2 inhibitor to people in a non-specialist setting if they have had a severe reaction, such as anaphylaxis, severe angioedema or an asthmatic reaction, to a non-selective NSAID.

Be aware that people with asthma who also have nasal polyps are likely to have NSAID-sensitive asthma unless they are known to have tolerated NSAIDs in the last 12 months.

REFERRAL TO SPECIALIST SERVICES

BETA-LACTAM ANTIBIOTICS

Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service if they:
- need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic **or**
- are likely of to need beta-lactam antibiotics frequently in the future, (for example, people with recurrent bacterial infections or immune deficiency).

Consider referring people to a specialist drug allergy service if they are not able to take beta-lactam antibiotics and at least 1 other class of antibiotic because of suspected allergy to these antibiotics.

LOCAL ANAESTHETICS

Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.

GENERAL REFERRAL

Refer people to a specialist drug allergy service if they have had:
- a suspected anaphylactic reaction (also see Anaphylaxis, NICE clinical guideline 134) **or**
- a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson Syndrome, toxic epidermal necrolysis).

NSAIDs

Refer people who need treatment with an NSAID to a specialist drug allergy service if they have had a suspected allergic reaction to an NSAID with symptoms such as anaphylaxis, severe angioedema or an asthmatic reaction.

GENERAL ANAESTHESIA

Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

DOCUMENTING AND SHARING INFORMATION WITH OTHER HEALTHCARE PROFESSIONALS

Recording drug allergy status

Document people's drug allergy status in their medical records using 1 of the following:
- 'drug allergy'
- 'none known'
- 'unable to ascertain' (document it as soon as the information is available).

If drug allergy status has been documented, record all of the following at a minimum:
- the drug name
- the signs, symptoms and severity of the reaction (see signs and allergic patterns above)
- the date when the reaction occurred.

Documenting new suspected drug allergic reactions

When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:
- the generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
- a description of the reaction (see signs and allergic patterns above)
- the indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
- the date and time of the reaction
- the number of doses taken or number of days on the drug before onset of the reaction
- the route of administration
- which drugs or drug classes to avoid in future.

Maintaining and sharing drug allergy information

Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.

Ensure that drug allergy status is documented separately from adverse drug reactions and that it is clearly visible to all healthcare professionals who are prescribing drugs.

Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see also providing information and support to patients opposite). Update the person's medical records or inform their GP if there is a change in drug allergy status.

Ensure that information about drug allergy status is updated and included in all:
- GP referral letters
- hospital discharge letters.

Carry out medicines reconciliation for people admitted to hospital in line with recommendations in Technical patient safety solutions for medicines reconciliation on admission of adults to hospital (NICE patient safety solutions guidance 1).

Documenting information after specialist drug allergy investigations

For recommendations on referral to specialist services see above.

After specialist drug allergy investigations, allergy specialists should document:
- the diagnosis, drug name and whether the person had an allergic or non-allergic reaction
- the investigations used to confirm or exclude the diagnosis
- drugs or drug classes to avoid in future.

PROVIDING INFORMATION AND SUPPORT TO PATIENTS

Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see documenting new suspected drug allergic reactions opposite). Record who provided the information and when.

Provide information in line with the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).

Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.

Advise people (and their family members or carers as appropriate) to carry information they are given about their drug allergy at all times and to share this whenever they visit a healthcare professional or are prescribed, dispensed or are about to be administered a drug.

Providing information and support to people who have had specialist drug allergy investigations

For recommendations on referral to specialist services see above.

Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:
- the diagnosis – whether they had an allergic or non-allergic reaction
- the drug name and a description of their reaction (see signs and allergic patterns above left)
- the investigations used to confirm or exclude the diagnosis
- drugs or drug classes to avoid in future
- any safe alternative drugs that may be used.

Explain to people in whom allergy to a drug or drug class has been excluded by specialist investigation that they can now take this drug or drug class safely and ensure that their medical records are updated.

5 Guideline summary

5.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 11 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual (2012).[125] The reasons behind selection of each of these recommendations are shown in the table linking the evidence to the recommendation in the relevant chapter.

Assessment

1. When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following boxes as a guide when deciding whether to suspect drug allergy.

- **Boxes 1–3 Signs and allergic patterns of suspected drug allergy with timing of onset[a]**

Box 1 Immediate, rapidly evolving reactions

Anaphylaxis – a severe multi-system reaction characterised by: • erythema, urticaria or angioedema **and** • hypotension and/or bronchospasm	Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)
Urticaria or angioedema without systemic features	
Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs [NSAIDs])	

Box 2 Non-immediate reactions without systemic involvement

Widespread red macules or papules (exanthem-like)	Onset usually 6–10 days after first drug exposure or within 3 days of second exposure
Fixed drug eruption (localised inflamed skin)	

Box 3 Non-immediate reactions with systemic involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: • widespread red macules, papules or erythroderma • fever • lymphadenopathy • liver dysfunction • eosinophilia	Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure

[a] Note that these boxes describe common and important presenting features of drug allergy but other presentations are also recognised

Toxic epidermal necrolysis or Stevens–Johnson syndrome characterised by: • painful rash and fever (often early signs) • mucosal or cutaneous erosions • vesicles, blistering or epidermal detachment • red purpuric macules or erythema multiforme	Onset usually 7–14 days after first drug exposure or within 3 days of second exposure
Acute generalised exanthematous pustulosis (AGEP) characterised by: • widespread pustules • fever • neutrophilia	Onset usually 3–5 days after first drug exposure
Common disorders caused, rarely, by drug allergy: • eczema • hepatitis • nephritis • photosensitivity • vasculitis	Time of onset variable

Documenting and sharing information with other healthcare professionals

Documenting new suspected drug allergic reactions

2. When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:
    - the generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
    - a description of the reaction (see recommendation 1)
    - the indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
    - the date and time of the reaction
    - the number of doses taken or number of days on the drug before onset of the reaction
    - the route of administration
    - which drugs or drug classes to avoid in future.

Maintaining and sharing drug allergy information

3. Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.
4. Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see also

recommendation 20). Update the person's medical records or inform their GP if there is a change in drug allergy status.

Providing information and support to patients

5. Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see recommendation 10). Record who provided the information and when.
6. Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.

Providing information and support to people who have had specialist drug allergy investigations

7. Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:
    - the diagnosis – whether they had an allergic or non-allergic reaction
    - the drug name and a description of their reaction (see recommendation 1)
    - the investigations used to confirm or exclude the diagnosis
    - drugs or drug classes to avoid in future
    - any safe alternative drugs that may be used.

Non-specialist management and referral to specialist services

General

8. Refer people to a specialist drug allergy service if they have had:
    - a suspected anaphylactic reaction (also see Anaphylaxis, NICE clinical guideline 134) **or**
    - a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson Syndrome, toxic epidermal necrolysis).

Non-steroidal anti-inflammatory drugs (including selective cyclooxygenase 2 inhibitors)

9. For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:
    - discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy)
    - consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.

Beta-lactam antibiotics

10. Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service 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).

General anaesthesia

11. Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

5.2 Full list of recommendations

Assessment

1. When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following boxes as a guide when deciding whether to suspect drug allergy.

Boxes 1–3 Signs and allergic patterns of suspected drug allergy with timing of onset[b]

Box 1 Immediate, rapidly evolving reactions

Anaphylaxis – a severe multi-system reaction characterised by: • erythema, urticaria or angioedema **and** • hypotension and/or bronchospasm	Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)
Urticaria or angioedema without systemic features	
Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs [NSAIDs])	

Box 2 Non-immediate reactions without systemic involvement

Widespread red macules or papules (exanthem-like)	Onset usually 6–10 days after first drug exposure or within 3 days of second exposure
Fixed drug eruption (localised inflamed skin)	

Box 3 Non-immediate reactions with systemic involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: • widespread red macules, papules or erythroderma • fever • lymphadenopathy • liver dysfunction • eosinophilia	Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure
Toxic epidermal necrolysis or Stevens–Johnson syndrome characterised by: • painful rash and fever (often early signs)	Onset usually 7–14 days after first drug exposure or within 3 days of second

[b] Note that these boxes describe common and important presenting features of drug allergy but other presentations are also recognised

• mucosal or cutaneous erosions • vesicles, blistering or epidermal detachment • red purpuric macules or erythema multiforme	exposure
Acute generalised exanthematous pustulosis (AGEP) characterised by: • widespread pustules • fever • neutrophilia	Onset usually 3–5 days after first drug exposure
Common disorders caused, rarely, by drug allergy: • eczema • hepatitis • nephritis • photosensitivity • vasculitis	Time of onset variable

2. Be aware that the reaction is more likely to be caused by drug allergy if it occurred during or after use of the drug and:
   - the drug is known to cause that type of reaction **or**
   - the person has previously had a similar reaction to that drug or drug class.
3. Be aware that the reaction is less likely to be caused by drug allergy if:
   - there is a possible non-drug cause for the person's symptoms (for example, they have had similar symptoms when not taking the drug) **or**
   - the person has gastrointestinal symptoms only.

Measuring serum tryptase after suspected anaphylaxis

4. After a suspected drug-related anaphylactic reaction, take 2 blood samples for mast cell tryptase in line with recommendations in Anaphylaxis (NICE clinical guideline 134).
5. Record the exact timing of both blood samples taken for mast cell tryptase:
   - in the person's medical records **and**
   - on the pathology request form.
6. Ensure that tryptase sampling tubes are included in emergency anaphylaxis kits.

Measuring serum specific immunoglobulin E

7. Do not use blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy in a non-specialist setting.

Documenting and sharing information with other healthcare professionals

Recording drug allergy status

8. Document people's drug allergy status in their medical records using 1 of the following:
    - 'drug allergy'
    - 'none known'
    - 'unable to ascertain' (document it as soon as the information is available).
9. If drug allergy status has been documented, record all of the following at a minimum:
    - the drug name
    - the signs, symptoms and severity of the reaction (see recommendation 1)
    - the date when the reaction occurred.

Documenting new suspected drug allergic reactions

10. When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:
    - the generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation
    - a description of the reaction (see recommendation 1)
    - the indication for the drug being taken (if there is no clinical diagnosis, describe the illness)
    - the date and time of the reaction
    - the number of doses taken or number of days on the drug before onset of the reaction
    - the route of administration
    - which drugs or drug classes to avoid in future.

Maintaining and sharing drug allergy information

11. Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.
12. Ensure that drug allergy status is documented separately from adverse drug reactions and that it is clearly visible to all healthcare professionals who are prescribing drugs.
13. Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see also recommendation 20). Update the person's medical records or inform their GP if there is a change in drug allergy status.
14. Ensure that information about drug allergy status is updated and included in all:
    - GP referral letters
    - hospital discharge letters

15. Carry out medicines reconciliation for people admitted to hospital in line with recommendations in Technical patient safety solutions for medicines reconciliation on admission of adults to hospital (NICE patient safety solutions guidance 1).

Documenting information after specialist drug allergy investigations

For recommendations on referral to specialist services see Chapter 12.

16. After specialist drug allergy investigations, allergy specialists should document:
    - the diagnosis, drug name and whether the person had an allergic or non-allergic reaction
    - the investigations used to confirm or exclude the diagnosis
    - drugs or drug classes to avoid in future.

Providing information and support to patients

17. Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see recommendation 10). Record who provided the information and when.
18. Provide information in line with the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).
19. Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.
20. Advise people (and their family members or carers as appropriate) to carry information they are given about their drug allergy at all times and to share this whenever they visit a healthcare professional or are prescribed, dispensed or are about to be administered a drug.

Providing information and support to people who have had specialist drug allergy investigations

For recommendations on referral to specialist services see Chapter 12.

21. Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:
    - the diagnosis – whether they had an allergic or non-allergic reaction
    - the drug name and a description of their reaction (see recommendation 1)
    - the investigations used to confirm or exclude the diagnosis
    - drugs or drug classes to avoid in future
    - any safe alternative drugs that may be used.
22. Explain to people in whom allergy to a drug or drug class has been excluded by specialist investigation that they can now take this drug or drug class safely and ensure that their medical records are updated.

Non-specialist management and referral to specialist services

General

23. If drug allergy is suspected:

- consider stopping the drug suspected to have caused the allergic reaction and advising the person to avoid that drug in future
- treat the symptoms of the acute reaction if needed; send people with severe reactions to hospital
- document details of the suspected drug allergy in the person's medical records (see recommendations 10 and 13)
- provide the person with information (see Chapter 10).

24. Refer people to a specialist drug allergy service if they have had:
    - a suspected anaphylactic reaction (also see Anaphylaxis, NICE clinical guideline 134) **or**
    - a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson Syndrome, toxic epidermal necrolysis).

Non-specialist management: Non-steroidal anti-inflammatory drugs (including selective cyclooxygenase 2 inhibitors)

25. Explain to people with a suspected allergy to a non-selective non-steroidal anti-inflammatory drug (NSAID) (and their family members or carers as appropriate) that in future they need to avoid all non-selective NSAIDs, including over-the-counter preparations.
26. For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:
    - discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy)
    - consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.
27. Do not offer a selective COX-2 inhibitor to people in a non-specialist setting if they have had a severe reaction, such as anaphylaxis, severe angioedema or an asthmatic reaction, to a non-selective NSAID.

Referral to specialist drug allergy services

28. Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service 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).
29. Consider referring people to a specialist drug allergy service if they are not able to take beta-lactam antibiotics and at least 1 other class of antibiotic because of suspected allergy to these antibiotics.
30. Refer people who need treatment with an NSAID to a specialist drug allergy service if they have had a suspected allergic reaction to an NSAID with symptoms such as anaphylaxis, severe angioedema or an asthmatic reaction.
31. Be aware that people with asthma who also have nasal polyps are likely to have NSAID-sensitive asthma unless they are known to have tolerated NSAIDs in the last 12 months.

32. Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.
33. Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.

5.3 Key research recommendations

5.3.1 Designing systems for documenting drug allergy

Which documentation strategies would be most clinically and cost effective to minimise the number of people who are re-exposed to drugs to which they have a suspected or confirmed allergy, looking in particular at:

- electronic health records that include features specifically designed to record and alert clinicians to drug allergy information, compared with systems without such features, **and**
- different formats for patient-held, structured drug allergy documentation?

5.3.2 Communicating information about drug allergy

In people with suspected or confirmed drug allergies, are patient-focused information strategies more effective than standard NHS practice in increasing people's likelihood of disclosing their drug allergy (or their suspected drug allergy) and therefore reducing the risk of being re-exposed to the affected drug?

5.3.3 Using selective cyclooxygenase 2 inhibitors in people with previous severe allergic reactions to non-selective non-steroidal anti-inflammatory drugs

Should all patients who have experienced a severe allergic reaction to a non-selective non-steroidal anti-inflammatory drug (NSAID) be assessed by specialist drug allergy services or should they be advised to take a selective cyclooxygenase 2 (COX-2) inhibitor without further investigations if clinically appropriate?

5.3.4 Oral antibiotic challenge for diagnosing antibiotic allergy in children

In children who have a suspected allergy to an antibiotic, is it clinically and cost effective to proceed directly (without prior skin or intradermal tests) to a diagnostic oral antibiotic challenge rather than referring them to specialist drug allergy services?

6 Assessment

When a new drug is started a patient may experience adverse symptoms for a variety of reasons. These may be related to the underlying disorder for which the patient was being treated, may be incidental and unrelated to the drug or disease, or they may be caused by the drug itself.

In cases of known non-immunologically mediated adverse reaction, for example, nausea or abdominal discomfort, the decision on whether to continue will be taken after discussion with the patient, and assessment of the severity of the reaction and the length of the remaining prescription course will be taken into account. If the patient has suffered a hypersensitivity reaction, however, the drug will almost invariably be stopped and if necessary an alternative drug sought. There can be considerable overlap between symptoms recognised from the adverse reaction profile of the drug and those resulting from hypersensitivity reaction. Each drug has a specific pattern of expected non-allergic symptoms and even immunologically mediated symptoms can follow a familiar pattern seen in previous patients. A correct diagnosis differentiating an allergic from a non-allergic reaction at the time of presentation should therefore allow safe future prescription and avoidance of the specific drug or drug class. Detailed documentation of the adverse reaction will also allow a more accurate specialist assessment if the patient requires the same or similar drug in future.

6.1 Review question: What is the clinical and cost effectiveness of clinical probability scores or algorithms in identifying or excluding drug allergies?

For full details see review protocol in Appendix C.

Table 6: Characteristics of review question

Population	Patients presenting with signs and symptoms of suspected drug allergy; patients with a record of a suspected drug allergy
Intervention	Clinical algorithms or prediction rules that assess likelihood or class patients by likelihood of having a drug allergy
Aim	To identify any signs and symptoms that are consistently used to assess the likelihood of a person having a drug allergy across algorithms currently in use
Study design	In the absence of RCTs, cohorts studies will be considered, particularly any multivariate studies used to derive the algorithms

6.2 Clinical evidence

6.2.1 Algorithms

We searched the literature for systematic reviews or any other study design that aimed to identify a set of signs and symptoms, usually in the form of a questionnaire or checklist (that is, an algorithm) to ascertain whether a person has a drug allergy. One systematic review (Agbabiaka et al. 2008[3]) was identified, as were 7 additional algorithm studies: Bousquet et al. 2009,[18] Caimmi et al. 2012,[23] Du et al. 2013,[38] Gallagher et al. 2011[52] (also known as the Liverpool algorithm), Gonzalez et al. 1992[56] (which was missing from Agbagiaka's systematic review), Son et al. 2011[154] and Trewin et al. 1991[161] (also missing from Agbagiaka's systematic review). Each of these studies describes the development of an algorithm in order to evaluate drug allergies. A further study was identified which updated 1 of the included algorithms (Arimone et al. 2013[5] updating the French Begaud et al. 1985[12] algorithm). This is added to the reference in Table 7.

The systematic review of algorithms by Agbabiaka et al. 2008[3] is considered to be at a moderate risk of bias according to the NICE systematic review checklist (since the quality of the included algorithms and probability scores was reported in a narrative manner and criteria for quality assessment were not explicitly described),but it considered algorithms for both adverse drug reactions and drug allergies. The authors included 26 algorithms in the systematic review. Six of these algorithms[64,77,80,106,158,174] were excluded from this review on the basis that they focused on adverse drug reactions (ADR) alone without the drug allergy being recorded as a subset of ADR.

The working definition of 'algorithm' from the identified systematic review was, "…a set of specific questions with associated scores for calculating the likelihood of a cause–effect relationship". The authors extracted criteria in the assessment of adverse drug reactions for 26 algorithms and probability scores and these are shown in Table 7 below for each of the included algorithms. The 12 categories for assessment provide a starting point for this review but were not explained fully. Therefore it was necessary in some cases to impute the meaning of individual categories.

The following categories were used (with brief explanations of how we interpreted them):

1. Time to onset or temporal sequence.
   Measurement of the time elapsed between taking medication and a reaction to develop.
2. Previous experience or information on drug.
   A previous experience with the drug or a previous reaction to the drug.
3. Alternative aetiological candidates.
   Ruling out other reasons for the reaction to the drug.
4. Drug level or evidence of overdose.
   Whether the correct dose was used.
5. Challenge.
   Assessment of what happens when the drug is introduced.
6. Dechallenge.
   Assessment of what happens when the person is taken off the drug.
7. Rechallenge.
   Assessment of what happens when the drug is reintroduced.
8. Response pattern to drug (symptoms).
   This point was unclear in the systematic review. We interpreted it to mean the clinical manifestation of the signs and symptoms that would be specific to the drug under investigation.
9. Confirmed by laboratory evidence.
   Whether laboratory tests have already been carried out.
10. Concomitant drugs.
    Whether there could be a potential drug interaction.
11. Background epidemiological or clinical information.
    For this category we focused on background epidemiology since clinical information was not clearly defined in the review.
12. Characteristics or mechanisms of adverse drug reaction.
    How this reaction is related to the drug under investigation and whether the reaction is plausible in light of the drug's mechanisms.

We also searched the literature for systematic reviews or any other study design that aimed to identify a set of signs and symptoms in the form of a probability score to ascertain whether a person has a drug allergy. The systematic review by Agbabiaka et al.[3] reviewed 4 probabilistic or Bayesian approaches to assessment of drug allergy.[70,92,94,109] One further study was identified (Theophile et al. 2013[160]). This additional study also included a comparison with other algorithms.

Furthermore, Agbabiaka et al. 2008[3] reviewed comparisons of algorithms. These are studies in which people with suspected drug allergies are assessed with more than 1 algorithm and the level of agreement (that is, congruency) between the assessments is then calculated. Table 10 summarises results of 6 comparative studies.[13,20,76,113,134,160] A further comparison study was added in the update of the systematic review.[160]

Agbabiaka et al. 2008[3] included a narrative analysis of 26 algorithms, but there was no explicit quality assessment of individual algorithms (they were appraised narratively). In the current review an explicit list of criteria was drawn up to assess the quality of the 6 additional algorithms that were identified from the search. In this checklist the quality of each of the following features was assessed (for these criteria please see section 3.3.6.4).

Using the format from Agbabiaka et al. 2008[3] used in Table 7, the 12 criteria were extracted for each of the 7 additional studies[18,23,38,52,56,154,161] included in the current review.

Table 7 below reproduces an amended version of the summary that is provided in Agbabiaka et al. 2008.[3] Studies which did not include drug allergy in the adverse drug reaction algorithms were excluded. Table 8 uses the same criteria to assess the additional algorithms identified in our search (with comments and quality assessment according to our checklist in the final 2 columns).

Table 11 summarises the frequency of the criteria across algorithms. Please also see the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix K.

Table 7: Criteria to assess the association between a reaction and a drug: studies included in the systematic review (adapted from Agbabiaka et al. 2008[3])

Author	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evidence of overdose	Chall-enge	Dechall-enge	Rechall-enge	Response pattern to drug	Confirm-ed lab evidence	Concom-itant drugs	Back-ground epi or clin info	ADR char or mech	Other
Begaud et al. 1985,[12] updated by Arimone et al. 2013[5]	✓	×	✓	✓	×	✓	✓	✓	✓	✓	×	✓	×
Benichou and Danan 1992[14]	✓	×	×	×	×	×	×	✓	✓	×	✓	×	×
Blanc et al. 1979[16]	✓	×	×	×	✓	×	×	×	✓	×	×	×	×
Castle 1984[24]	✓	×	✓	✓	×	×	×	✓	×	✓	✓	×	×
Cornelli 1984[30]	✓	×	×	✓	×	×	✓	✓	×	✓	×	×	×
Danan and Benichow 1993[31]	✓	×	✓	×	×	×	×	✓	✓	×	✓	×	×
Dangoumau et al. 1978[32]	×	×	✓	✓	×	✓	✓	✓	×	×	×	×	×
Emanueli and Sacchetti 1980[40]	✓	✓	✓	×	✓	×	✓	✓	×	×	×	×	×
Evreux et al. 1982[45]	✓	✓	✓	×	×	✓	×	×	×	×	×	×	×
Hoskins and	✓	×	×	×	×	✓	✓	×	×	×	✓	✓	×

Author	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evidence of overdose	Chall-enge	Dechall-enge	Rechall-enge	Response pattern to drug	Confirm-ed lab evidence	Concom-itant drugs	Back-ground epi or clin info	ADR char or mech	Other
Mannino 1992[65]													
Hsu and Stoll 1993[67]	×	✓	×	✓	×	×	✓	✓	×	×	×	×	×
Irey 1976[73]	✓	×	×	✓	×	✓	✓	✓	✓	×	×	×	×
Jones 1982[75]	×	✓	×	✓	×	×	✓	✓	×	×	×	×	×
Koh and Shu 2005[82]	✓	×	✓	✓	✓	×	✓	×	×	×	×	×	×
Kramer et al. 1979[87]	✓	×	✓	✓	✓	×	✓	✓	×	×	×	×	×
Lagier et al. 1983[91]	×	×	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓
Naranjo et al. 1981[121]	×	✓	✓	×	✓	×	✓	✓	✓	×	×	×	×
Stephens 1984[157]	×	×	✓	✓	×	×	✓	✓	✓	✓	×	×	×
Turner 1984[162]	✓	×	×	×	✓	✓	×	×	×	×	✓	×	×
Venulet et al. 1980[167]	×	✓	×	✓	×	✓	✓	×	×	✓	×	×	✓

Abbreviations:

TTO or temp seq:	time to onset or temporal sequence
Prev exp or drug info:	previous experience or information on drug
Alter aetiologies:	alternative aetiological candidates (underlying illnesses, new illnesses, non-drug therapies and diagnostic tests and procedures)
Dechallenge:	drug discontinued or reduced in dosage
Response pattern to drug:	clinical manifestation – symptoms improve with treatment
Background epi or clin info:	background epidemiological or clinical information
ADR char or mech:	characteristics or mechanisms of adverse drug reaction
Other:	other factors

Table 8: Criteria to assess the association between a reaction and a drug: studies not included in the systematic review (adapted from Agbabiaka et al. 2008[3] with additional notes and quality ratings in the final 2 columns)

Author, population, setting	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evid-ence of OD	Chall-enge	De-chall-enge	Re-chall-enge	Res-ponse pattern to drug	Confirm-ed lab evidence	Con-com-itant drugs	Back-ground epi or clin info	ADR char or mech	Other	Quality
Bousquet et al. 2009[18] – ENDA classification Setting: ENDA (European Network for Drug Allergy) collaboration	✓	✓	✓	×	×	×	×	✓	✓	✓	×	✓	Acute (up to 24 hours) versus delayed reactions (more than 24 hours)	High
Caimmi et al. 2012[23] Population & setting: Consecutive patients referred to Allergy Department University Hospital, Montpelier, France	✓	✓	×	×	×	×	×	✓	×	×	✓	✓	Immediate (up to 6 hours) or non-immediate (more than 6 hours)	High
Du et al. 2013[38]; Population: neonatal patients Setting: USA & Canada	✓	×	✓	✓	×	✓	✓	✓	×	✓	✓	×	Algorithm validated and performed better than Naranjo scale with Kappa and ICC scores of 0.76 and 0.62 compared to 0.31 and 0.43	Moderate. Not appropriate for GP practice; no precise definition of DA
Gallagher et al. 2011[52] – Liverpool	✓	✓	✓	×	✓	×	✓	✓	✓	✓	×	×	In comparison with the Naranjo	High

Author, population, setting	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evid-ence of OD	Chall-enge	De-chall-enge	Re-chall-enge	Res-ponse pattern to drug	Confirm-ed lab evidence	Con-com-itant drugs	Back-ground epi or clin info	ADR char or mech	Other	Quality
algorithm Based on case reports in children's hospitals in the UK													algorithm more patients can be classified as 'definite' causal relationship	
Gonzalez et al. 1992[56] Population: patients with suspected beta-lactam reaction Setting: Allergy Department, Hospital Universitario Reina Sofia, Cordoba, Spain	×	×	×	×	✓	×	×	✓	✓	×	×	×	Scores based on 3 parameters only: clinical symptoms, aetiology and lab tests	Moderate. No validation; all factors not considered; no precise definition of DA
Son et al. 2011[154] Population: patients with cutaneous ADRs Setting: South Korea	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	×	To evaluate the accuracy of a Korean algorithm which was developed because, '…algorithms used in foreign countries with different genetic backgrounds, investigation and level of	High

Author, population, setting	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evid-ence of OD	Chall-enge	De-chall-enge	Re-chall-enge	Res-ponse pattern to drug	Confirm-ed lab evidence	Con-com-itant drugs	Back-ground epi or clin info	ADR char or mech	Other	Quality
													awareness for ADRS and as such they might not be suitable for use in Korea.' This algorithm correlated well with Naranjo.	
Trewin 1991[161] Population: elderly patients with suspected drug allergy Setting: Pharmacy Department, Royal Devon & Exeter Hospital	×	×	✓	×	×	✓	×	✓	✓	×	✓	×	Included in this algorithm for the elderly was also 'medication compliance' and 'source of medication' details. In the number and type of ADRS identified only 2 were 'rash' and there was no reference to drug allergy.	Moderate Single author of algorithm; no validation; no precise definition of DA; all factors not considered.

Abbreviations:

TTO or temp seq:	time to onset or temporal sequence
Prev exp or drug info:	previous experience or information on drug
Alter aetiologies:	alternative aetiological candidates (underlying illnesses, new illnesses, non-drug therapies and diagnostic tests and procedures)
Dechallenge:	drug discontinued or reduced in dosage
Response pattern to drug:	clinical manifestation – symptoms improve with treatment
Background epi or clin info:	background epidemiological or clinical information
ADR char or mech:	characteristics or mechanisms of adverse drug reaction
Other:	other factors

Quality Assessment: 9 criteria for quality assessment. Scoring of positive responses: 7–9 high quality; 4–6 moderate quality; 1–3 low quality

6.2.2 Probability scores

Bayesian methods have been proposed to provide a formal inferential framework for causality in the assessment of drug allergy and adverse drug reactions. It is mathematically based upon calculating a ratio (the posterior odds) between 2 probabilities both of which are conditional on the same background and case information: that a given drug caused an adverse event versus that an alternative cause is responsible.

Despite the benefits of repeatability, transparency, explicitness, completeness, balancing of case data and no arbitrary limiting of information on the assessment, this method of causation analysis can be time consuming and may require significant use of resources and complex calculations.

The same categories were used as those described for the algorithms.

Agbabiaka et al. 2008[3] included a narrative analysis of the probabilistic and Bayesian approaches, but there was no explicit quality assessment of individual algorithms.

Table 9 below is adapted from the summary that is provided in Agbabiaka et al.[3]

Table 9: Probabilistic or Bayesian approaches to causation used

Author	TTO or temp seq	Prev exp or drug info	Alter aetio-logies	Drug level or evidence of overdose	Chall-enge	Dechall-enge	Rechall-enge	Response pattern to drug	Confirm-ed lab evidence	Concom-itant drugs	Back-ground epi or clin info	ADR char or mech	Other
Hutchinson et al. 1991[70]	✓	×	×	×	×	×	✓	✓	✓	✓	×	×	×
Lanctot et al. 1995[93]	✓	✓	×	×	×	✓	✓	×	×	×	✓	✓	×
Lane et al. 1987[94]	✓	×	×	×	×	×	✓	✓	✓	×	×	✓	×
Mashford 1984	✓	×	×	×	×	×	×	×	✓	×	×	×	✓
Theophile et al. 2013[160]	✓	×	✓	×	×	✓	✓	✓	✓	✓	×	×	✓

Abbreviations:

TTO or temp seq: time to onset or temporal sequence

Prev exp or drug info:	*previous experience or information on drug*
Alter aetiologies:	*alternative aetiological candidates (underlying illnesses, new illnesses, non-drug therapies and diagnostic tests and procedures)*
Dechallenge:	*drug discontinued or reduced in dosage*
Response pattern to drug:	*clinical manifestation – symptoms improve with treatment*
Background epi or clin info:	*background epidemiological or clinical information*
ADR char or mech:	*characteristics or mechanisms of adverse drug reaction*
Other:	*other factors*

6.2.3 Comparative studies

The conclusion of the systematic review by Agbabiaka et al. 2008[3] was that "…no single algorithm is accepted as the 'gold standard,' because of the shortcomings and disagreements that exist between them." We have reviewed 6 studies[13,20,76,113,134,160] which compare the most commonly used algorithms for drug allergy and provide kappa statistics as a measure of congruency. A summary of the statistical conclusions of the comparative studies is provided in Table 10 below.

Table 10: Studies comparing algorithms

Reference	Algorithms compared	Sensitivity	Specificity	Positive (negative) predictive values	Concordance with allergy diagnosis	Concordance with other algorithms
Benahmed et al. 2005[13]	Begaud Jones Naranjo	Begaud: 8.3% Jones: 50% Naranjo: 0%	Begaud: 98.3% Jones: 53.3% Naranjo: 100%	Begaud: 50.9% (83.5%) Jones: 18.5% (83.4%) Naranjo: 0% (100%)	Begaud: No concordance, k=0.12 Jones: No concordance, k=0.14 Naranjo: No concordance, k=0.14	Jones and Naranjo: perfect concordance (k=1) but the Jones method showed a substantial trend in favour of higher scores for the cases. Begaud: No concordance (k=0)
Busto et al. 1982[20]	Kramer (ASS) Naranjo (APS)					High inter-rater reliability when both methods were used: Scores obtained with APS were highly correlated with those obtained with ASS by both raters: r=0.86 and r=0.81 respectively. Time spent using the ASS was slightly but significantly longer than that using the APS (9.52 (±3.02) minutes versus 8.94 (±3.51) minutes)

Reference	Algorithms compared	Sensitivity	Specificity	Positive (negative) predictive values	Concordance with allergy diagnosis	Concordance with other algorithms
Kane-Gill et al. 2012[76]	Jones Kramer Naranjo					The level of agreement between algorithms have kappa values all >0.7 between individual instruments with the Naranjo criteria versus Kramer algorithm having the highest kappa score, which is considered excellent agreement.
Michel & Knodel 1986[113]	Kramer Naranjo					Agreement between Kramer and Naranjo was 67% with kappa=0.43; Kramer versus Jones was 67% agreement with k=0.48; Naranjo versus Jones was 64% agreement with k=0.28.
Pere et al. 1986[134]	Begaud Emanueli Kramer Naranjo	Weightings of criteria: Criteria are not highly sensitive (0.41<Sens<0.70)	Weightings of criteria: Criteria are not highly specific (0.18<Spec<0.63)			Concordance between methods is better than with chance but never more than moderately (0.40<kappa<0.60). Kramer versus Naranjo (k=0.51).
Theophile et al. 2013[160]	Probabilistic method Liverpool Naranjo	Probabilistic method: 0.96 Naranjo and Liverpool were identical with 2 scores calculated depending on whether 'possible' was considered in favour or disfavour of drug causation: 1 or 0.42	Probabilistic method: 0.56 Naranjo and Liverpool: 0.11 or 0.89	Probabilistic method: 0.92 (0.71) Naranjo and Liverpool: 0.86 or 0.95 (1 or 0.22)	Logistic method gave results closer to expert opinion and the Liverpool and Naranjo algorithms depended on the interpretation of the 'possible' category of cases.	Naranjo and Liverpool performed similarly with more cases of 'definites' in the latter.

6.2.4 Most commonly used algorithm criteria

For the current review we used the Agbabiaka et al. 2008[3] findings for 20 algorithms which included drug allergy as part of the evaluation of ADR, the 5 probabilistic or Bayesian studies in Agbabiaka et al. 2008,[3] and the 7 additional algorithms added into this review, to assess how frequently different causality criteria appeared across all of the algorithms (see Table 11). The assessment criteria were ranked as follows:

Table 11: Frequency causality criteria were used across 32 algorithms and probability scores (25 from the systematic review and 7 added in the current review)

Assessment criteria	Included in algorithms, n/total (%)
1. Time to onset or temporal sequence	24/32 (75%)
2. Response pattern to drug (clinical response)	24/32 (75%)
3. Rechallenge	22/32 (69%)
4. Alternative aetiological candidates	17/32 (53%)
5. Confirmed by laboratory evidence	16/32 (50%)
6. Drug level or evidence of overdose	15/32 (47%)
7. Dechallenge	14/32 (44%)
8. Background epidemiological or clinical information	12/32 (38%)
9. Previous exposure or drug information	12/32 (38%)
10. Concomitant drugs	12/32 (38%)
11. Challenge	10/32 (31%)
12. ADR characteristics or mechanism	8/32 (25%)

The evidence shows that none of the criteria are used consistently in all of the algorithms. This includes 'time to onset or temporal sequence' and 'response pattern to drug (clinical response)' which were only used as assessment criteria in 24 (75%) of the 32 algorithms. Questions about drug challenge and ADR characteristics or mechanisms featured least frequently across algorithms, only occurring in 10 and 8 of 32 algorithms (31% and 25%), respectively.

Agbabiaka et al. 2008[3] also reviewed comparisons of algorithms which were updated here. These are studies in which people with suspected drug allergies are assessed with more than one algorithm and the level of agreement (that is, congruency) between the assessments is then calculated. Congruencies showed the whole range from 0% to 100% agreement with no agreement between the Begaud and Kramer or Jones in one study and a 100% agreement between Kramer and Jones in the same study. Even the same comparisons sometimes had very different levels of agreement across comparisons (for example, comparisons of Kramer and Jones showed perfect agreement in one study and only moderate agreement, 67%, in another).

6.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

6.4 Evidence statements

Clinical

- Assessment criteria: moderate quality evidence from 32 algorithms and probability scores (according to quality of the included systematic review and the quality of the additional algorithms) indicated no clear criteria that were used consistently to assess whether a person has a drug allergy. The most frequently used criteria were 'time to onset or temporal sequence' and 'response pattern to drug'.
- Assessment comparisons: there were highly variable levels of agreement between algorithms ranging from no agreement (0%) to a perfect level of agreement (100%) with some inconsistencies in results for the same comparisons in different studies. In all comparisons the Naranjo algorithm was used as one of the comparators or the only reference standard. The second most frequent comparator was the Kramer algorithm.

Economic

- No relevant economic evaluations were identified.

6.5 Recommendations and link to evidence

Recommendation

1. When assessing a person presenting with possible drug allergy, take a history and undertake a clinical examination. Use the following boxes as a guide when deciding whether to suspect drug allergy.

Boxes 1–3 Signs and allergic patterns of suspected drug allergy with timing of onset[c]

Box 1 Immediate, rapidly evolving reactions

Anaphylaxis – a severe multi-system reaction characterised by: • erythema, urticaria or angioedema **and** • hypotension and/or bronchospasm	Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)
Urticaria or angioedema without systemic features	
Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs [NSAIDs])	

Box 2 Non-immediate reactions without systemic involvement

Widespread red macules or papules (exanthem-like)	Onset usually 6–10 days after first drug exposure or within 3 days of second exposure
Fixed drug eruption (localised inflamed skin)	

[c] Note that these boxes describe common and important presenting features of drug allergy but other presentations are also recognised

Box 3 Non-immediate reactions with systemic involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by: • widespread red macules, papules or erythroderma • fever • lymphadenopathy • liver dysfunction • eosinophilia	Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure
Toxic epidermal necrolysis or Stevens–Johnson syndrome characterised by: • painful rash and fever (often early signs) • mucosal or cutaneous erosions • vesicles, blistering or epidermal detachment • red purpuric macules or erythema multiforme	Onset usually 7–14 days after first drug exposure or within 3 days of second exposure
Acute generalised exanthematous pustulosis (AGEP) characterised by: • widespread pustules • fever • neutrophilia	Onset usually 3–5 days after first drug exposure
Common disorders caused, rarely, by drug allergy: • eczema • hepatitis • nephritis • photosensitivity • vasculitis	Time of onset variable

2. **Be aware that the reaction is more likely to be caused by drug allergy if it occurred during or after use of the drug and:**
   - **the drug is known to cause that type of reaction or**
   - **the person has previously had a similar reaction to that drug or drug class.**

3. **Be aware that the reaction is less likely to be caused by drug allergy if:**
   - **there is a possible non-drug cause for the person's symptoms (for example, they have had similar symptoms when not taking the drug) or**
   - **the person has gastrointestinal symptoms only.**

Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: mortality, number of repeat drug allergic reactions, length of hospital stay, acute admission or readmission into secondary care, number of contacts with healthcare professionals, inappropriate avoidance of drugs, health-related quality of life. The group noted that no evidence was identified that directly addressed the effectiveness of algorithms in terms of the clinical outcomes specified, but the evidence instead focused on causality criteria with associated scores in developing an algorithm.
Trade-off between clinical benefits and harms	The group agreed that the benefit of an algorithm for the assessment of signs and symptoms is that it can help in identifying whether the reaction observed is likely to be caused by a drug. However, in the group's opinion, the key potential harm of recommending the use of an algorithm to people with a suspected drug allergy is the poor predictive value provided by algorithms. Specifically, the lack of absolute prediction of whether the person presenting with a suspected drug allergy is experiencing an allergic reaction or not and the risk of clinicians providing false reassurance was a key concern. The GDG noted that signs and symptoms of drug allergy in children may differ from those in adults, and typical patterns suggesting an allergic reaction to a drug may not apply in a child's case. For example, non-specific rashes are more common in children and these are usually not due to drug allergy, whilst severe cutaneous reactions are less common in children. The GDG also recognised that people of certain ethnicities and those with certain comorbidities such as cystic fibrosis or HIV are at higher risk of allergic reaction to specific drugs or drug classes.
Economic considerations	No relevant economic evidence was identified. The GDG did not prioritise this question for original economic analysis. The GDG agreed that the proposed assessment would most likely be carried out as part of an initial GP (or other non-drug allergy specialist) assessment, but could take longer than current practice (which generally involves noting an adverse reaction, rather than assessing the reaction and investigating the possibility of an allergy). Therefore, there may be a small increase in initial cost. However, the GDG felt that appropriate assessment would be of great clinical benefit to the person with a suspected drug allergy, as it would be likely to improve the accuracy of diagnosis. Accurate diagnosis will improve quality of life, and reduce the later costs associated with incorrect labelling of drug allergy (such as those incurred by patients who are unnecessarily given alternative second-line drugs, which are often more expensive and less effective than the first-line option). Appropriate assessment using the recommendations above will therefore assist selection of the appropriate treatment strategy for each person with a suspected drug allergy, and therefore promote economic efficiency of the clinical pathway. The GDG agreed that carrying out the assessment when the patient first presents with a potential allergic reaction would lead to the best clinical outcomes, as details of the reaction are likely to be documented more accurately than if left to a later stage. Overall the GDG agreed that the benefits (improvements in quality of life and reduced future costs) of the signs and symptoms checklist would outweigh the small upfront cost of a longer initial consultation.
Quality of evidence	The aim of the review of algorithms was to identify common signs and symptoms that indicate whether a person may have a drug allergy. The evidence showed that a number of the algorithms did not specify such patterns but focused on the types of questions that physicians need to consider when trying to identify whether the drug caused the reaction.

	The NICE quality assessment tool for systematic reviews was applied to the published systematic review. A further tool was designed to assess the quality of algorithm studies added to this review. The studies included in the review were assessed as good to moderate quality. However, since the algorithms that were reviewed did not always address signs and symptoms directly, the evidence was given less value in drawing up the recommendations. The GDG advised that not all the algorithms reviewed were applicable to primary care as they required too much time for a GP to use during standard consultations, required challenge testing, or did not result in a final clinical decision for managing a patient. The GDG noted that the algorithms included in the review looked at adverse drug reactions and not at drug allergy specifically and were not assessed for effectiveness in clinical settings.
Other considerations	The GDG concurred with the conclusion of the Agbabiaka[3] systematic review that clinical judgement is still required when using an algorithm as a decision-making tool, and that no single algorithm is accepted as a gold standard. The GDG noted that the Naranjo[121] and Kramer[86,87] studies were the most commonly referred to within the literature, and the study by Jones which compared the 2 favoured the Naranjo algorithm.[121] The European Network for Drug Allergy questionnaire (Bousquet 2009[18]) was a large study designed for use by GPs and was assessed as being of high quality. However, no study had addressed how effective these tools were within a clinical practice setting, and the GDG thought that none of the algorithms were practical for use in general practice or other non-specialist settings. Most of the studies did not assess the clinical effectiveness (that is, directly leading to improved patient outcomes) of algorithms against each other or against other methods of diagnosis. This evidence would have been included but no further studies were identified. The GDG noted the difficulty of capturing the wide range of drugs and reactions to drugs in a single decision-making tool, and that as drug allergy is a subset of adverse drug reaction, it was difficult to identify drug allergy using an adverse drug reaction questionnaire such as the tools produced by Kramer[86,87] or the European Network for Drug Allergy (ENDA).[18] The GDG suggested alternatives which may be more effective, such as checklists, pathways or flow charts. The GDG questioned the helpfulness of a probability score as used in the ENDA questionnaire[18] because it does not lead to a decision for the clinician. However, the group did think a checklist of common symptoms may be helpful and further agreed that any decision tool should ideally be short, easy to use and include a score that would determine the action to be considered by the clinician. The group cited the use of the CHADS2 system[120] (congestive heart failure, hypertension, age ≥75 years, type 2 diabetes and previous stroke or transient ischemic attack), which is used as a predication rule for atrial fibrillation. Although no suitable scoring system was identified from the review, the development of a validated algorithm or decision rule including a scoring system for use within non-specialist settings would be a helpful guide in assessing and managing people who have had a suspected allergic reaction to a drug. The GDG agreed the common signs and symptoms listed in the ENDA study[18] could be adapted and used as a basis for the recommendations. The GDG acknowledged the questions used within the Naranjo paper are for use within a specialist setting,[121] however they believed some of these were also relevant for use within a non-specialist setting and would be a helpful addition to the recommendations as a part of the initial assessment and decision-making process undertaken by the

	clinician. Providing timings of when signs and symptoms are likely to occur after exposure to a drug was thought to be helpful when making an assessment. The group arrived at the timings given in the recommendations through informal consensus based on their clinical experience and knowledge of the literature in this area. The GDG noted that currently, adverse reactions are listed in the information provided with most drugs and these reactions are categorised from common reactions, to less common reactions and rare reactions.

7 Measuring serum tryptase after suspected anaphylaxis

The measurement of serum tryptase after allergic reactions remains under-used, even after life-threatening episodes of anaphylaxis. Acute elevation of serum tryptase indicates degranulation of mast cells which occurs either due to an IgE-mediated mechanism, for example with penicillin allergy, or may result from direct degranulation of mast cells through non-IgE-mediated means, for example with NSAIDs or opiates. The rise in tryptase levels starts to be detected in serum within minutes of anaphylaxis but the level will gradually revert to normal over the next 6–24 hours depending on the height of the increase and often correlates with the severity of the anaphylaxis.

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by rapidly developing life-threatening problems involving the airway (pharyngeal or laryngeal oedema), breathing (bronchospasm with tachypnoea), circulation (hypotension or tachycardia), or a combination of these. In most cases, there are associated skin and mucosal changes. However, some of the symptoms of anaphylaxis may be due to other causes, such as an acute cardiovascular or respiratory event. Therefore, measurement of serum tryptase taken in a timely manner can help to identify whether the cause is due to anaphylaxis and if the level is acutely elevated this should reduce the requirement for unnecessary investigations of other causes. An acute increase in serum tryptase also indicates that the reaction was potentially life-threatening and, therefore, indicates a need to identify the drug that caused the reaction and any potential cross-reacting agents in order to reduce further risk.

7.1 Review question: What is the clinical and cost effectiveness of serum tryptase testing compared with reference standard tests for the diagnosis of an anaphylactic reaction due to suspected drug allergy?

For full details see review protocol in Appendix C.

Table 12: Characteristics of review question

Population	Patients presenting with signs and symptoms of anaphylaxis
Intervention (index test)	Serum tryptase test taken during an acute reaction
Comparison (reference standard)	• Other methods of confirming diagnosis of drug allergy such as skin tests, oral challenge test or a more complete diagnostic work up • No serum tryptase done during acute reaction
Outcomes	1. Pre-test probability 2. Sensitivity 3. Specificity 4. Positive predictive value (PPV) 5. Negative predictive value (NPV) 6. Number of cases missed (false negative)
Study design	Diagnostic cohort studies

7.2 Clinical evidence

The utility of serum tryptase for the diagnosis of anaphylaxis has been published in the context of NICE clinical guideline 134: Anaphylaxis (2011).[124] We conducted a full search on this topic and identified 1[59,59] study that was not included in the anaphylaxis guideline and a further study[141] published since the guideline which were both added to this review. All studies included in the Anaphylaxis guideline that were not specific to drug allergy were excluded. After this exclusion 2 studies[104,112] remained from the Anaphylaxis guideline as well as the additional studies.[59,141]

Evidence was divided by serum tryptase threshold:

- Two studies provided evidence for testing at a medium threshold at peak (11.4 and 12 microgram/litre) and
- Three studies provided evidence for testing at a high threshold at peak (24 and 25 microgram/litre)

Any information about the timing of testing was also summarised and is presented in the GRADE evidence profile (Table 14).

Evidence from these studies are summarised in the clinical GRADE evidence profile below (Table 14). See also the study selection flow chart in Appendix E, sensitivity and specificity forest plots in Appendix J, study evidence tables in Appendix H and exclusion list in Appendix K.

Table 13: Summary of studies included in the review

Study	Objective, index test and reference standard	Population	Outcomes
Malinovsky et al. 2008[104]	Aim to evaluate incidence of hypersensitivity reactions during anaesthesia by using histamine and tryptase measurements and allergological investigations to investigate suspected or unexplained reactions. Reference standard: Clinical diagnosis and immunological tests	Patients with suspected hypersensitivity reaction to anaesthetics (29 general, 2 regional) at University Hospital Nantes from May 2001 to April 2003 (hypersensitivity reaction determined if presented with cutaneous symptoms, that is urticaria or angioedema) isolated or in association with other clinical symptoms like bronchospasm, hypotension, or cardiovascular collapse or if circulatory inefficacy in close relation with anaesthetic drug injection in absence of other explanation. Patients with IgE-mediated hypersensitivity reactions: Median age: 43 years (range: 8–80) 45% (10/22) male, 55% (12/22) female Patients without IgE-	With 12 micrograms/ litre threshold: Sens: 63.6% (95% CI 40.7% to 82.8%) Spec: 100% (when calculated by analyst specificity was 88.9% with 95% CI 51.8% to 99.7%) With 25 micrograms/ litre threshold: Sens: 40.9% (95% CI 20.7% to 63.6%) Spec: 100% (95% CI 66.4% to 100%) With 12 micrograms/ litre threshold: PPV: 100% NPV: 53% (when calculated by analyst these values were PPV: 93.3% (95% CI 68.1% to 99.8%) NPV: 50% (95% CI 24.7 to 75.3%)) With 25 micrograms/

Study	Objective, index test and reference standard	Population	Outcomes
		mediated hypersensitivity reactions: Median age: 45 years (range: 19–78) 56% (5/9) male, 44% (4/9) female	litre threshold: PPV: 100% (95% CI 66.4% to 100%) NPV: 41% (95% CI 20.7% to 63.6%)
Mertes et al. 2003[112]	Aim to survey allergic and non-immunologically mediated reactions during anaesthesia, description of clinical characteristics, and identification of possible factors and responsible drugs. Reference standard: Clinical diagnosis and skin prick test or IgE	Patients with adverse reaction during anaesthesia in France between Jan 1999 and December 2000	With 25 micrograms/ litre threshold: Sens: 64% (95% CI 56.4% to 71.1%) Spec: 89.3% (95% CI 80.6% to 95.0%) With 25 micrograms/ litre threshold: PPV: 92.6% (95% CI 86.3% to 96.5%) NPV: 54.3% (95% CI 45.7% to 62.8%)
Harboe et al. 2005[59]	Aims of this study were to describe a patient population that developed peri-anaesthetic anaphylaxis in the years 1996–2001 and to evaluate the standardised protocol used for allergy follow-up examination at 1 allergy outpatient clinic in Western Norway. Index test: Serum tryptase was measured using the Pharmacia UniCAP FEIA system (Pharmacia Diagnostics). Researchers attempted to obtain serum samples at 3 time points: before, within 2 hours after and on the day after the reaction. Levels were considered increased if the 2-hour serum concentration was above 24 micrograms/litre or 3 times that of the background concentration. Reference standard: Skin prick tests performed in duplicate.	Patients who had an anaphylactic reaction to general anaesthesia	A significant acute (within 2 hours) increase of serum tryptase accompanied 40 (48.2%) of the anaphylactic reactions. In 25 cases (30.1%), no increase was detected, but for 15 of these, the time interval between reaction and blood sampling was not specified. From 18 (21.7%) of the events, 2-hour serum samples were not obtained.
Sala-Cunill et al. 2013[141]	Aim was to determine sequential serum tryptase concentration in patients with anaphylaxis, both during the acute episode and at baseline, and to evaluate its usefulness in the diagnosis of anaphylaxis and as a marker related to the clinical severity of the reaction. Index test: Tryptase was measured using the UniCAP-Tryptase fluoroimmunoassay	Patients with a confirmed clinical diagnosis of anaphylaxis by allergist and serum tryptase drawn during anaphylaxis (mixed population).	Overall sensitivity of serum tryptase in drug allergy patients only: 33/51 (65%).

Study	Objective, index test and reference standard	Population	Outcomes
	(Phadia, now Thermo Fisher Scientific). A serum tryptase concentration ≥11.4 micrograms/litre was considered high. Reference standard: Skin prick test		

Abbreviations: FEIA: fluoroenzymoimmunoassay; NPV: negative predictive value; PPV: positive predictive value; sens: sensitivity; spec: specificity

Table 14: Clinical evidence profile: serum tryptase

Number of studies	Study designs	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity – median (95% CI)	Specificity – median (95% CI)	PPV – median (95% CI)	NPV – median (95% CI)	Timing	Quality
Mast cell tryptase medium threshold at peak (11.4 and 12 micrograms/litre)												
2	Cross-sectional	82	very serious risk of bias[a]	N/A[b]	no serious indirectness	very serious imprecision[c]	64% (41–83%); 65% (50–78%)	89% (52–100%)	93%	50%	In 1 study 30–60 minutes (positive readings were on average 5.25 times higher than after 24 hours). In the other study 65 people with samples taken at 2 hours and 40 (61%) had increased serum tryptase.	VERY LOW
Mast cell tryptase high threshold at peak (24 and 25 micrograms/litre)												
3	Cross-sectional	355	very serious risk of bias[a]	serious inconsistency[c]	no serious indirectness	very serious imprecision[c]	41% (21–64%); 64% (56–71%); 62% (49–73%)	100% (66–100%); 89% (81 – 95%)	93%; 100%	54%; 41%	One study is the same as above. In another study readings were taken at 2 hours. In the third study peak levels were reached between 1–2 hours, but average level remained elevated at 4–6 hours. 20/45 had high levels at 4–6 hours and 9/27 at 12–24 hours.	VERY LOW

Only 3 studies contributed to the test at each threshold and results were not pooled. All extractable values are given in the table rather than 1 median value.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The overall risk of bias for each outcome was assessed according to the risk of bias for the majority of the evidence.

(b) There was insufficient data to derive a 2×2 table and assess level of inconsistency (sensitivity and specificity could only be calculated in 1 study).

(c) Inconsistency and imprecision were assessed by inspection of the sensitivity/specificity paired forest plots and the confidence intervals of these accuracy measures. Inconsistency was assessed based on the point estimate (ranging from below chance level, 41% to moderate sensitivity, 64%), The judgement of precision was based on the confidence interval in sensitivity / specificity. A range of between 10% and 20% was considered to be seriously imprecise whereas more than 20% was considered to be very seriously imprecision. Judgements reflected the poorest quality rating.

7.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Costs from the Protein Reference Unit in Sheffield[71] are used as example costs: the cost per test is £36.67, therefore the total cost estimate of tryptase testing is £73.34. It is noted that this figure does not capture the full economic impact of tryptase testing, which would include the time of a healthcare professional to administer the tests, as well as downstream cost and quality of life implications of using the tests.

7.4 Evidence statements

Clinical

- Very low quality evidence from 4 observational studies (n=480) showed good level of specificity (89–100% where it was possible to derive this measure) regardless of threshold. Sensitivity was low (median 64% regardless of threshold). There was large uncertainty around the estimate and it is therefore unclear how to interpret this. Information on timing was not available in all studies, but when described peak levels were reached up to 2 hours.

Economic

- No relevant economic evaluations were identified.

7.5 Recommendations and link to evidence

Recommendations	**Measuring serum tryptase after suspected anaphylaxis** **4. After a suspected drug-related anaphylactic reaction, take 2 blood samples for mast cell tryptase in line with recommendations in Anaphylaxis (NICE clinical guideline 134).** **5. Record the exact timing of both blood samples taken for mast cell tryptase:** **• in the person's medical records and** **• on the pathology request form.** **6. Ensure that tryptase sampling tubes are included in emergency anaphylaxis kits.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: pre-test probability, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number of cases missed (false negatives), number of cases mislabelled (false positives). A positive test result (acutely elevated serum tryptase) would be highly

	suggestive of drug allergy and should direct further investigation. Therefore the specificity of the test result is important, that is, false positive results should be low. For this condition it is also paramount not to miss cases and therefore if a person tests negative on tryptase the probability that he or she had an anaphylactic reaction should be lower. The sensitivity of the test result is therefore also important. However, the GDG agreed that a normal serum tryptase, taken acutely does not exclude drug allergy. Therefore the sensitivity measurement of the test may not be weighted as the most important outcome.
Trade-off between clinical benefits and harms	The evidence indicated that the proportion of people who have the condition when they tested positive (PPV) was high. Specificity values were also generally very high (between 89% and 100%). However since sensitivity was variable and modest, many people without elevated levels of tryptase did have anaphylactic reactions due to drug allergy. They would therefore be missed at this time point and might receive the drug again in the future before referral to specialists. Moreover, people with negative tryptase results might wrongly believe that the reaction was unrelated to the drug they had received.
Economic considerations	No relevant economic evidence was identified. The GDG identified diagnostic tests (serum tryptase and serum specific IgE) as the second highest priority area for original economic analysis. However, the GDG concluded that modelling would not be feasible for this review question due to the lack of necessary clinical data linking diagnostic test results with future clinical outcomes such as further allergic reactions, alternative drugs taken, hospitalisation and resource use. The GDG therefore considered the unit costs of these tests and discussed the likely impact on downstream resources and health related quality of life. Mast cell tryptase blood testing has an additional cost, including the analysis of 2 tests (£77) and additional healthcare professional time to collect the samples. Tryptase results are highly useful to GPs and specialists when they are later considering whether a person has a drug allergy and deciding what further tests are required. They are also helpful in informing the healthcare professional on what action should be taken in managing any drug allergy. The GDG believed that correctly administered and reported tryptase testing would be likely to reduce future resource use by reducing the extent of further investigations needed into possible drug allergy in an individual. Tryptase testing would also increase clinicians' abilities to correctly diagnose an individual as having or not having a drug allergy. This could reduce future hospitalisations due to further allergic reactions in those with drug allergy, thereby reducing costs and improving quality of life, and reducing excess spending on unnecessary alternative drugs in those without drug allergy. The GDG therefore agreed that mast cell tryptase testing is likely to be cost effective. For tryptase testing to take place on a routine basis the incorporation of blood sample tubes for tryptase testing into anaphylaxis kits would be an efficient method of ensuring these very low cost items are available to clinicians at the point at which they are needed.
Quality of evidence	The quality of the evidence was judged to be very low for all thresholds of serum tryptase. Some studies had poor definitions of the hypersensitivity reaction or recorded time intervals poorly. A variety of different tests was also used (for example, radioimmunoassays (RIA), Immunotech; UniCAP system, Pharmacia) which may also limit the generalisability of these results. The statistical measures did show wide confidence intervals and it is therefore difficult to estimate confidently how accurate the tests were as confidence intervals ranged sometimes from 41% to 83%.
Other considerations	Tryptase testing is currently usually carried out in secondary care. Serum tryptase tests will remain stable for 24 hours at room temperature and

	therefore the GDG considered that it was a suitable test to be carried out within a GP setting and would assist in the future management of the person if referred on to secondary care. The group agreed that the test is currently underutilised within primary care, but needs to be undertaken in a timely manner and records of timings kept in the person's notes. No studies were identified that directly reported evidence for the use of serum tryptase testing in children. The GDG discussed whether any specific recommendations were needed for children and concluded that the recommendations would apply to all age groups. The GDG agreed that sample tubes should be incorporated into anaphylaxis kits and resuscitation trolleys, as this would provide a practical prompt to take a blood sample at the time of the reaction and would make the process easier and quicker. The GDG discussed the timing of tryptase testing with peak elevations usually reported around 1–2 hours after the reaction. The utility of testing beyond 4 hours was debated. One study (Sala-Cunhill et al. 2013[141]) reported patients with elevated tryptase at different time points beyond 2 hours, but this was in a mixed population of a small group of people with drug allergy reactions. In this study the number of people with tryptase levels recorded later than 2 hours was small (a mixed allergy group of 45 people at 4–6 hours and 27 at 12–24 hours). This indicates that serum tryptase may remain elevated beyond 4 hours, but this study was not large enough to be conclusive. The study reported elevated tryptase in the 1–2 hour timeframe as significantly higher than at any other time point. The other studies all investigated reactions to anaesthesia and did not report any timings other than a 2-hour time point. The NICE Anaphylaxis guideline[124] recommends that the test should be carried out preferably within 2 hours and not beyond 4 hours in order to encourage people to carry out the test early. Although a raised tryptase may occur beyond the 4-hour period, this would usually only be in a small percentage of people. The decision around timing of the tests in the Anaphylaxis guideline was made by consensus, and so the GDG discussed whether the same view would be held by health professionals now. The GDG noted that the test was more likely to be done within a shorter time period in a hospital emergency setting, and that after 4 hours the patient may have been moved and so there may be an increased chance the test would not be undertaken at all and cases may be missed. The recommendations for serum tryptase testing in the Anaphylaxis guideline are valid for those with a suspected drug reaction and have therefore been referred to within this guideline.

8 Measuring serum specific immunoglobulin E (IgE)

In this section we have considered the clinical and cost effectiveness of serum specific IgE testing for the diagnosis of drug allergy. Serum specific IgE testing is only available for reactions to a limited number of drugs, including: amoxicillin, ampicillin, cefaclor, chlorhexidine, morphine, penicillin and suxamethonium. The sensitivity and specificity of each of these tests in predicting whether a patient with a history of drug allergy is either allergic or non-allergic have been considered in order to evaluate whether this test could be used within a non-specialist setting such as a GP's surgery. This is the only non-acute test that can be undertaken in a non-specialist setting. For alternative tests such as skin prick testing or drug challenges the individual would need to be referred to specialist drug allergy services for investigation.

8.1 Review question: What is the clinical and cost effectiveness of serum specific IgE testing compared with reference standard tests in the diagnosis of drug allergy for the following drugs?

- amoxicillin
- ampicillin
- cefaclor
- chlorhexidine
- morphine
- penicillin G
- penicillin V
- suxamethonium

For full details see review protocol in Appendix C.

Table 15: Characteristics of review question

Population	Patients presenting with signs and symptoms of suspected drug allergy Patients with a record of suspected drug allergy
Intervention (Index test)	Serum specific IgE test for the following agents: • Ampicillin • Amoxicillin • Cefaclor • Chlorhexidine • Morphine • Penicillin G • Penicillin V • Suxamethonium
Comparison (reference standard)	• Other methods of confirming diagnosis of drug allergy such as skin tests, oral challenge test or a more complete diagnostic work • No serum specific IgE test (follow-up)
Outcomes	1. Pre-test probability 2. Sensitivity 3. Specificity 4. Positive predictive value (PPV) 5. Negative predictive value (NPV) 6. Number of cases missed (false negative)

Study design	Diagnostic cohort studies

8.2 Clinical evidence

We searched for diagnostic cohort and case–control studies as well as case series for the utility of serum specific IgE testing. Fourteen studies were identified for this review.[17,48,49,54,63,84,85,95,137,144,145,150,166,170] Evidence from these papers is summarised in the clinical GRADE evidence profile below (Table 17). See also the study selection flow chart in Appendix E, sensitivity and specificity forest plots in Appendix J, study evidence tables in Appendix H and exclusion list in Appendix K.

The evidence in this review is presented by class of drug as follows: beta-lactam antibiotics, neuromuscular blocking agents and chlorhexidine.

The IgE tests used and the study populations were variable and therefore a diagnostic meta-analysis was not carried out. The quality of studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) criteria.

Table 16: Summary of studies included in the review: beta-lactam antibiotics

Study	Intervention, comparison	Population	Outcomes
Blanca et al. 2001[17]	Index test Pharmacia CAP System FEIA serum specific IgE has a range of 0.35–100 kUA/litre with a cut-off value of ≥0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test. Reference standard Skin prick tests; intradermal tests in all subjects. Controlled challenge in those who were skin test negative and in whom only 1 episode of clinical symptoms has occurred.	Patients attending the clinical outpatient department before the skin test procedure n=74 drug allergy patients in 3 groups: Group 1 comprised 19 subjects with an immediate reaction to benzyl penicillin (BP) or amoxicillin (AX) and were skin test positive to amoxicillin or benzylpenicilloyl (BPO) independently of positivity to ampicillin (AMP) and minor determinant mixture (MDM). Group 2 comprised 29 subjects with an immediate reaction to an AX derivative, were skin test positive to AX determinants and negative to BPO and had good tolerance to BP; Group 3 comprised 26 subjects with an immediate reaction to penicillin or AX who were skin test negative to all penicillin derivatives used in the study. 2 control groups of 55 patients were included: Group 4 comprised 25 patients with a clinically documented non-IgE-mediated reaction to penicillin. Subjects who	Results for Groups 1–3 by hapten benzylpenicilloyl (BPO) and amoxicilloyl (AXO) BPO: TP: 24 FP: 1 FN: 50 TN: 54 Sensitivity: 32% Specificity: 98% AXO: TP: 32 FP: 1 FN: 42 TN: 54 Sensitivity: 43% Specificity: 98% BPO+AXO TP: 37 FP: 2 FN: 37 TN: 53

Study	Intervention, comparison	Population	Outcomes
		developed maculopapular or exanthemic reactions with an interval greater than 6 hours and usually within 24–48 hours after taking the drug were included in this group. Immediate skin tests to BPO, AX AMP and MDM had to be negative; Group 5 comprised 30 subjects with no history of allergic reaction to beta-lactams, a negative skin test to BPO, MDM, AX and AMP and good tolerance to BP and AX.	
TaFontaine et al. 2007[49]	Index test Pharmacia CAP System FEIA serum specific IgE has a range of 0.35–100 kUA/litre with a cut-off value of ≥0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test. The beta-lactam c1 (penicilloyl G), c6 (amoxicillin), c5 (ampicillin) and c7 (cefaclor) covalently coupled to ImmunoCap interact with the specific IgE in the serum samples tested. RAST testing by Research Unit for Allergic Diseases, Carlos Haya Hospital, Malaga, Spain. Reference standard Skin tests with different beta-lactams and drug provocation tests.	Patients who developed a reaction to a beta-lactam <6 hours after drug intake and exhibited either urticaria alone or anaphylaxis without shock (urticarial and another non-cutaneous symptom) or anaphylaxis with shock.	Whole population CAP FEIA: Sensitivity: 16.7% Specificity: 93.3% PPV: 45.5% NPV: 77.1% RAST: Sensitivity: 50.0% Specificity: 73.3% PPV: 38.5% NPV: 81.5%
Holm & Mosbech 2011[63]	Index test IgE ImmunoCAP FEIA system (Phadia, Uppsala, Sweden) with a cut off value of 0.35 kUA/litre. Reference standard Penicillin challenge test	Patients with clinical reaction to penicillin and negative IgE were offered a challenge with penicillin V, penicillin G or both	A patient with a history of a mild reaction to penicillin that occurred more than 15 years previously and with no detectable serum IgE antibodies to penicillin V, penicillin G, amoxicillin or ampicillin would have only a 0.4% risk for reacting when given penicillin V or G in a clinical setting. NPV: 97.6%
Kraft & Wide 1976[85]	Index test RAST technique by Wide, Bennich & Johnsson. Results	Patients seen either in the 2nd Department of Dermatology, University of	The benzylpenicilloyl specific RAST showed an overall correlation of 95.1 % with PPL

Study	Intervention, comparison	Population	Outcomes
	were considered as negative when the activity was less than mean plus 2 SD for negative controls. Reference standard Skin tests	Vienna or during consultant visits to other University or City hospitals in Vienna divided into 3 groups: Group A: Included 31 patients seen during the first 24 hours of acute reactions to penicillin and tested with available test systems including skin tests later on. Group B: Included 33 patients with history of reactions to penicillin 18 days to 11 years previously and tested by the available test systems including skin tests. Group C: Included 15 patients who were seen in the first 24 hours of acute reactions to penicillin, but tested by in vitro methods only.	performed skin tests. TP: 18 FP: 3 FN: 5 TN: 38 Sensitivity Group A and B combined: 78% Specificity Group A and B combined: 93% Positive predictive value Groups A and B combined: 86% Negative predictive value Groups A and B combined: 88%
Kraft et al. 1977[84]	Index test RAST by Pharmacia Diagnostics. Results were expressed in Phadebas RAST classes 0, 1, 2, 3 and 4 according to a reference system established by running four reference sera (A, B, C and D) with reference discs during each assay in parallel to the unknown samples. In this study class 0 was considered to be a negative RAST result. Reference standard Skin prick tests and intradermal tests.	Patients seen either in the 2nd Department of Dermatology, University of Vienna or during consultant visits to other University or City hospitals in Vienna divided into 4 groups: Group A: Included 69 patients examined within 2 days of acute reaction to penicillin and who were tested for circulating specific IgE and by skin tests. Group B: Included 49 patients with history of reactions to penicillin in the period 3 weeks–5 years before the study and who were tested for circulating specific IgE and by skin tests. Group C: Included 76 patients who were examined during the first 2 days of acute reactions to penicillin but tested by in vitro tests only. Group D: Included 10 patients who exhibited penicillin allergy which was proved by skin tests in the period 2–5 years before the study and who were tested by in vitro tests.	Group A: TP: 16 FP: 0 FN: 3 TN: 50 Sensitivity: 84.2% Specificity: 100% Agreement between RAST and skin test: 95.7% Group B: TP: 9 FP: 0 FN: 7 TN: 33 Sensitivity: 56.3% Specificity: 100% Agreement: between RAST and skin test: 82.5% In Group D 10 patients had proven penicillin allergy 2–5 years before the study. 4 of 10 had showed a positive reaction to RAST: Sensitivity: 40%
Qiao et al.	Index test	Patients recruited from 2 Chinese hospitals divided into	Group B:

Study	Intervention, comparison	Population	Outcomes
2005[137]	Radioallergosorbent test (RAST) Reference standard Intradermal tests in all subjects with benzylpenicillin G at a concentration of 500 U/ml.	3 groups: Group A with historical positive skin test; Group B with immediate positive skin test; Group C with a negative skin test.	TP: 75 FN: 47 The positive rate (sensitivity) of specific IgE antibodies in 259 patients was 62.2%. Of these, the positive rates of specific IgE antibodies in Group A, B, and C were 62.7%, 61.5% and 63%. In 122 patients with immediate positive skin test (Group B), the positive rate of specific IgE was increased with the degree of positive skin test. Where the degrees of skin test were + (5–8 mm), 2+ (8–10 mm), 3+ (10–12 mm) and 4+ (>12 mm), the positive rates of specific IgE were 45.7, 57.1, 85.2 and 100% respectively.
Sanz et al. 1996[145]	Index test Pharmacia CAP System FEIA serum specific IgE has a range of 0.35–100 kUA/litre with a cut-off value of 0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test. Reference standard Skin test	Sera from patients who had been diagnosed with adverse reaction to beta-lactams and a history very suggestive of drug allergy.	85% of cases were specific IgE negative against Penicillin G, Penicillin V and ampicillin and 44% against amoxicillin. Skin test versus beta-lactam specific IgE Sensitivity 31.81% Specificity 88.57%
Sanz, Gamboa & De Weck, 2002[144]	Index test Pharmacia CAP System FEIA serum specific IgE has a range of 0.35–100 kUA/litre with a cut-off value of ≥0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test was used against penicilloyl G, penicilloyl V, ampicillin and amoxicillin. Reference standard Skin prick tests; intradermal tests in all subjects. Challenge in some patients with negative skin tests.	Patients presenting with immediate symptoms after beta-lactam.	Group 1: Results for 5 subgroups: Groups 1a: Patients clinically reacting to benzylpenicillin (BP) or amoxicillin (AX) and with positive skin tests to BP-derived reagents and to AX: 33% positivity (sensitivity) for BP and 33% positivity for AX. Group 1b: Patients with AX as the culprit drug but skin tests only positive to BP-derived reagents AND Group 1c: Patients with BP as the culprit drug and skin tests only positive to BP derived reagents AND Group 1d: 1 patient with BP as the culprit drug and the skin test paradoxically positive to AX: 35% positivity (sensitivity) for

Study	Intervention, comparison	Population	Outcomes
			BP and 22% positivity for AX. Also, 1 subgroup 1e of 6 patients reacting specifically to CEs. Total sensitivity in Group 1: 38% positive to BP and 17% positive to AX. Group 2: Results for 2 subgroups Group 2a: Skin test positive to AX/AMPI (ampicillin), BP not done Group 2b: Skin test positive to AX/AMPI and negative to BP. Total sensitivity in Group 2: 26% positive to BP and 32% positive to AXO. Group 3: Results for 16 cases presenting with an immediate clinical reaction to AX but with negative skin tests. Total sensitivity in Group 3: 19% Finally, in the group of 30 control patients, 4 had a positive CAP test resulting in a specificity of 87%.
Silva et al. 2009[151]	Index test Pharmacia CAP System (Phadia)serum specific IgE has a range of 0.35–100 kUA/litre with a cut-off value of ≥0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test. Reference standard Skin prick tests; intradermal tests if skin prick tests were negative. When skin tests and specific IgE were both negative, drug challenge with the suspected beta-lactam was performed.	Patients referred to Drug Allergy Division with history of beta-lactam hypersensitivity	Only 33 patients had full range of testing. Only patients with negative skin testing and negative IgE received oral challenge. As there were no IgE positive patients in this cohort, only NPV could be calculated. NPV: 93.9%
Vega et al. 1994[166]	Index test RAST – radiolabeled substance uptake test using discs treated with PG and AX. Reference standard Skin prick test, intradermal or	Patients with history of an immediate allergic reaction to amoxicillin (AX) and good tolerance of penicillin G (PG).	All 54 patients were either skin test or challenge test positive to AX. TP: 22 FP: 0 FN: 33 TN: 0

Study	Intervention, comparison	Population	Outcomes
	drug provocation tests.		Sensitivity of RAST for AX: 40% Specificity of RAST for AX: unable to calculate
Vultaggio et al. 2009[170]	Index test CAP system FEIA (Phadia, Uppsala, Sweden) for specific IgE antibodies. Serum in this sample was analysed for IgE towards the hapten c1 (penicilloyl G), c2 (penicilloyl V), c5 (ampicilloyl) and c6 (amoxicilloyl). Serum samples were considered positive when one or more hapten positivities occurred. 2 available commercial tests were performed (old and new CAP) characterised by different cut-off values of positivity (0.35 and 0.10 kUA/litre, respectively). Reference standard Skin prick test, intradermal test or both.	Patients with history of suspected immediate ADR to beta-lactams in the past year and a positive skin test.	Diagnostic performance of new and old CAP system for beta-lactam allergy: Sensitivity (95% CI): New test 0.85 (0.69 to 0.95) Old test 0.44 (0.27 to 0.62) Specificity (95% CI): New test: 0.54 (0.44 to 0.63) Old test 0.80 (0.72 to 0.87)
Summary of studies included in the review: neuromuscular blocking agents			
Study	**Intervention, comparison**	**Population**	**Outcomes**
Fisher & Baldo 2000[48]	Index test Radio immune assay for morphine and radio immune assay for specific IgE Reference standard Intradermal skin testing	Patients defined as experiencing anaphylaxis on the basis of a positive serum mast cell tryptase and positive skin test to one or more Neuromuscular Blocking Agents (NMBAs) divided into 4 groups: Group 1 Patients who had an elevated serum mast cell tryptase level and showed a positive skin test to at least 1 NMBA Group 2 Patients who had an elevated serum mast cell tryptase level and showed a positive skin test to a drug other than a NMBA Group 3 Patients who had suspected anaphylaxis but a serum mast cell tryptase level that was not elevated and skin tests to NMBDs were negative	Group 1 results only: Positive skin test and positive specific IgE RIA: 47/69 (68%) Positive skin test and positive morphine RIA: 67/69 (97%).

Study	Intervention, comparison	Population	Outcomes
		Group 4 Patients who had suspected anaphylaxis, serum mast cell tryptase levels were not elevated and no skin testing was performed	
Laroche et al. 2011[95]	Index test Quaternary ammonium morphine [QAM] ImmunoCAP; Phadia AB, Uppsala, Sweden. The detection limit was 0.10 kUA/litre. The cut-off serum concentration was 0.35 kUA/litre. Reference standard Skin prick tests and intradermal skin tests.	French patients who reacted during anaesthesia, 2001–2007: Group A: 57 reactors were selected on the basis of immediate reactions after NMBA injection, increased concentrations of histamine or tryptase, and a positive skin test to the administered NMBA Group B: 57 reactors with negative skin test to NMBAs during the same period.	Overall results: TP: 48 FP: 14 FN: 9 TN: 43 Overall sensitivity of 84.2% Overall specificity of 75.4%. PPV 77.4% NPV 82.7%
Summary of studies included in the review: chlorhexidine			
Study	**Intervention, comparison**	**Population**	**Outcomes**
Garvey et al. 2007[54]	Index test Chlorhexidine ImmunoCAP (Phadia AB) a cut-off value of ≥0.35 kUA/litre for a positive test and <0.35 kUA/litre for a negative test. Reference standard Skin prick tests in all subjects. Intradermal tests if prick test was negative.	22 patients with strong suspicion of allergy to chlorhexidine because of repeated or delayed reactions and results of initial skin testing.	Sensitivity: 91.7% Specificity: 100% PPV: 100% NPV: 91%

Abbreviations: AMP: ampicillin; AX: amoxicillin; AXO: amoxicilloyl group; BP: benzyl penicillin; BPO: benzylpenicilloyl group; CAP: Pharmacia CAP system; FEIA: fluoroenzymoimmunoassay; FN: false negative; FP: false positive; kUA/litre: kilounits of allergen per litre; MDM: minor determinant mixture; NMBA: neuromuscular blocking agent; NPV: negative predictive value; PPV: positive predictive value; RAST: radioallergosorbent test; RIA: radioimmunoassay; SD: standard deviation; TN: true negative; TP: true positive

Table 17: Clinical evidence profile: serum specific IgE – beta-lactam antibiotics, neuromuscular blocking agents, chlorhexidine

Number of studies	Study designs	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity – range, median (95% CI)	Specificity – range, median (95% CI)	PPV – range, median (95% CI)	NPV – range, median (95% CI)	Quality
Serum IgE (for beta-lactams)											
11	Cohort, case–control and case series	1624	serious risk of bias[a]	serious inconsistency[b]	no serious indirectness	very serious imprecision[c]	Range 30–85%, median 54% (33–73%)	Range 54–100%, paired median 76% (67–83%)	Range 32–95%, paired median 32%	Range 42–98%, paired median 89%	VERY LOW
Serum IgE (for neuromuscular blocking agents)											
2	Cohort	461	very serious risk of bias[a]	N/A[d]	N/A[d]	very serious imprecision[c]	84% (72–93%)	75% (62–86%)	77%	83%	VERY LOW
Serum IgE (for chlorhexidine)											
1	Case series	22	very serious risk of bias[a]	N/A[d]	N/A[d]	N/A[e]	92%	100%	100%	91%	VERY LOW

GRADE was conducted with emphasis on test sensitivity and NPV (proportion of people with a positive test who have drug allergy and proportion of people with a negative test result who do not have drug allergy, respectively) as this was the primary measure discussed in decision-making. The median sensitivity was identified and then the paired specificity, PPV and NPV were reported respectively.

(a) Risk of bias was assessed using the QUADAS-2 checklist. The overall risk of bias for each outcome was assessed according to the risk of bias for the majority of the evidence.

(b) Inconsistency was assessed by inspection of the paired sensitivity and specificity forest plots. Reasons for heterogeneity between studies include type of IgE test or study population (for example, type of beta-lactam allergy).

(c) The judgement of precision was based on visual inspection of the confidence region in the sensitivity and specificity plots. A range of 10% was considered to be seriously imprecise whereas 20% or more was considered to be very seriously imprecise.

(d) There was insufficient data to assess level of inconsistency (sensitivity and specificity could only be calculated in 1 study).

(e) Imprecision could not be assessed because confidence intervals were not provided in the study.

8.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Costs from the Protein Reference Unit in Sheffield[71] are used as example costs: the cost per allergen-specific IgE test is £14.30. It is noted that this figure does not capture the full economic impact of IgE testing, which would include the time of a healthcare professional to administer the test, as well as the downstream cost and quality of life implications of using the test.

8.4 Evidence statements

Clinical

Serum specific IgE – beta-lactam antibiotics

- Very low quality evidence from 11 observational studies (n=1624) indicated very variable results in terms of sensitivity and specificity. Specificity was generally higher than sensitivity indicating that the test is better at 'ruling in' than 'ruling out' beta-lactam allergy. However, imprecision was too high to draw clear conclusions about the test accuracy of this test.

Serum specific IgE – neuromuscular blocking agents

- Very low quality evidence from 2 observational studies (n=461) indicated relatively high levels of misclassification with sensitivity 84% and specificity 75%. The confidence region was large and only 1 result could be clearly extracted. It is therefore difficult to draw clear conclusions about this test in clinical practice.

Serum specific IgE – chlorhexidine

- Very low quality evidence from 1 observational study (n=22) indicated high levels of test accuracy. However, the number of participants in this study was small and it is therefore unclear whether this result is representative until further research is conducted.

Economic

- No relevant economic evaluations were identified.

8.5 Recommendations and link to evidence

Recommendations	**Measuring serum specific immunoglobulin E** **7. Do not use blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy in a non-specialist setting.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: pre-test probability, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number of cases missed (false negatives), number of cases mislabelled (false positives). The rate of false negatives represents the proportion of people with a drug allergy in whom allergic reactions will be missed by serum specific IgE testing; the GDG considered this outcome to be significant. Test sensitivity (the proportion of people with drug allergy who have a positive test) is therefore also an important outcome. However, the group also agreed that specificity is important in order that people who do not have an allergy do not falsely receive a positive test result and as a consequence no longer receive the drugs they require or are switched to less effective medication.
Trade-off between clinical benefits and harms	The GDG agreed that many people with penicillin allergies will receive false negative IgE test results. The evidence was consistent with low levels of diagnostic test sensitivity shown. The group acknowledged that for beta-lactam antibiotics IgE testing has poor negative predictive values, and there was concern that people with suspected drug allergies may be falsely reassured. However, specificity and positive predictive values were on the whole higher indicating that people who do not have drug allergies would have a high probability of having a negative test, and conversely a high percentage of people with a positive test result go on to be diagnosed with drug allergy. There was less evidence on testing for neuromuscular blocking agents or chlorhexidine. However, studies reported better sensitivity and negative predictive value results compared to IgE testing for beta-lactams. This seems to suggest that fewer people are missed by using serum specific IgE in these cases.
Economic considerations	No relevant economic evidence was identified. The GDG identified diagnostic tests (serum tryptase and serum specific IgE) as the second highest priority area for original economic analysis. However, the poor diagnostic accuracy shown by IgE testing in the clinical evidence for this review meant that economic modelling, even if feasible, was not necessary for the GDG's decision-making and so original analysis was not conducted. Carrying out this test incurs costs associated with the time of a GP or nurse, the laboratory test itself, and follow-up appointments. The clinical evidence reveals low sensitivity and specificity values of serum specific IgE tests, and therefore the results of these tests are not deemed a sufficient result on which to base a diagnosis of drug allergy. The GDG were particularly concerned with the high levels of false negative results revealed by the clinical evidence. False negatives could lead to repeat reactions, which in turn have a high cost (emergency admission) and a significant impact on quality of life. False positive results could also have an economic impact, as a person may unnecessarily receive an alternative drug when a drug is needed in future. Alternative treatments are generally less effective and sometimes more expensive than first-line treatments. These economic considerations need to be balanced against the potential benefit from obtaining a true result. If the results of the test could be relied

	upon, people receiving a true positive result could take up an appropriate management strategy and the cost of referral would be saved. Likewise, true negatives would not need to avoid the drug in question any longer. However, the clinical evidence has revealed such inaccuracy in the test results that the results of serum specific IgE tests cannot be considered conclusive. Diagnoses cannot be based on this test alone regardless of the outcome, and therefore the additional cost of these tests is an inefficient use of resource. The GDG therefore agreed that serum specific IgE tests are unlikely to be cost effective when used on their own in a non-specialist drug allergy setting.
Quality of evidence	Quality was assessed as very low for all evidence (serum IgE testing for beta-lactams, neuromuscular blocking agents or chlorhexidine). This was mainly due to the heterogeneity of study populations, type of test used, type of allergy and imprecision of the accuracy measures. Many studies also did not use a gold standard (drug provocation test) as a reference point. As the evidence came from highly selective populations the GDG agreed that it was difficult to extrapolate results to the whole population of people with drug allergies and were therefore cautious about making specific recommendations.
Other considerations	The GDG agreed that these tests do not have proven utility in primary care as results could be open to misinterpretation due to poor sensitivity. Additionally the tests do not add much to diagnosis made from a clinical history. The group recognised that in a specialist setting this test would not be used in isolation but may be used in addition to a skin prick test and the clinical presentation. The group noted that many allergic drug reactions are not IgE-mediated and the tests do not include all immunoreactive epitopes. The GDG noted that RAST (radioallergosorbent test) is an old technology and no longer used. None of the studies addressed testing in children and none were conducted in primary care settings. The GDG noted that serum specific IgE for diagnosing drug allergy may be useful in the specialist setting in conjunction with clinical history and other allergy investigations.

9 Documenting and sharing information with other healthcare professionals

Analysis of patient safety incidents reported to the National Reporting and Learning System (NRLS) over 8 years (2005–2013) identified 18,079 incidents involving drug allergy. There were 6 deaths, 19 'severe harms', 4980 'other harms' and 13,071 'near misses' reported.[130] The majority of these incidents involved a drug that was prescribed, dispensed or administered for a patient with a previously known allergy to the drug or drug class. The drug allergy information was usually documented in the clinical notes, medication card or allergy (red band) bracelet. Despite this a drug was administered to a patient known to be allergic resulting in moderate to severe harm in more than 1000 cases. This shows that documentation is often ineffective or is ignored and avoidable incidents due to drug error are common.

Patients who have experienced drug allergy are not routinely provided with written information. Therefore, with the passage of time, details of the drug, possible cross-reacting agents and an indication of the severity of the reaction become increasingly difficult to recall. In some clinical situations, it may be necessary to re-expose the patient, for example where an alternative drug is less effective or the patient has multiple drug allergies. However, with incomplete clinical details of the original reaction it may not be possible to make a judgement on whether a reaction was immunologically mediated, and hence assess the risk of an allergic reaction on re-exposure.

Detailed clinical information is also needed for patients referred for specialist investigation of drug allergy and that process may be prolonged, requiring additional consultations, if documentation is incomplete.

9.1 Review question: What are the most clinically and cost effective documentation strategies for communicating drug allergy information across all NHS services to prevent patients from receiving drugs to which they are allergic?

For full details see review protocol in Appendix C.

Table 18: PICO characteristics of review question

Population	Patients with drug allergies and healthcare professional involved in the care of patients with drug allergies
Interventions	• Patient-held records or information worn by patients • Hospital-based notices worn by patients (such as coloured arm bands) • Automated messages (for example, screensavers) • Mandatory reporting of drug allergy status in paper or electronic medication records • Mandatory documentation of details related to adverse drug reactions • Mandatory documentation of details of any investigations for suspected drug allergy • Position of the information or alerts relating to drug allergy status in medical or electronic records • Design of drug charts • Use of Summary of Care Records • Computerised physician or prescriber order entry systems (CPOE)
Comparisons	No intervention or another intervention alone or in combination
Outcomes	• Medication errors (inappropriate prescription or administration of drugs)

	• Number of repeat drug allergic reactions (including patient-reported episodes) • Inappropriate avoidance of drugs • Health-related quality of life
Study design	Any study design other than case studies, comments and letters to the editor

Following discussion with the GDG, it was recognised that documentation completion rate would be an informative surrogate outcome for medication errors. Absence of information on drug allergy from documentation could be erroneously interpreted as absence of drug allergy and this can potentially lead to prescriber errors. Therefore, we have included studies that did not necessarily report rates of medication errors but reported how complete or accurate the recorded data were in documentation.

Due to the large number of interventions (some further interventions are described in the full protocol in Appendix C) it was decided to prioritise higher quality evidence if necessary. Pharmacy reviews and reconciliation were not classified as documentation strategies and studies describing these interventions were excluded.

9.2 Clinical evidence

In this review we aimed to identify documentation strategies that ensure that drug allergy status is clearly indicated and effective in minimising medication errors. Documentation includes the way physicians record the drug allergy status as well as how the person with the allergy might indicate that he or she has a drug allergy (such as bracelets, for example). Thirty-three observational studies[1,8,9,15,19,27,29,41-44,58,62,66,69,89,97,103,105,110,111,118,129,132,135,146,147,152,153,155,156,165,175] and 2 randomised trials[60,159] were included in this review.

Studies can be broadly divided into 2 main categories:

- Twenty-one studies[1,8,9,15,19,27,42-44,66,69,89,97,103,111,129,132,155,156,159,165,173] investigated the effectiveness of computerised physician or prescriber order entry systems (CPOE) and other computer systems that aim to limit errors in medication prescriptions for people with drug allergies.
  - A subset of these studies[66,69,89,159] describes the frequency at which allergy alerts are ignored or overridden and the reasons for this.
  - The computerised order systems included medication lists which sometimes suggested dosage and route as well as various levels of checking systems to alert physicians to a variety of issues including drug allergies (usually also including drug–drug interactions, drug–laboratory problems and redundant medication checks).
- Nine studies[29,41,60,62,105,110,132,152,175] assessed the design of pro formas and charts to indicate drug allergy status and their effectiveness in minimising drug errors.
  - Examples of such charts were provided in 4 studies.[29,62,105,152] Three of those included a box with an 'allergy' heading and 1 of them provided additional prompts for type of reactions (however this study used the form both for assessment and documentation). The other studies referred to design, structure or designated areas without additional detail.

Evidence from the 2 randomised controlled trials[60,159] was combined with evidence from observational studies. This was due to major problems with study design and directness of outcomes in the trials. The trial by Tamblyn et al. (2008), investigating 'on demand' versus 'automatic' alerts, refers to error rates and overrides without a specific group of drug allergy errors. In the trial by Harris et al. (2002) the structured pro forma intervention was only used by a small minority of participants.

Evidence for the main 2 categories (computerised, structured charts) are summarised in the clinical evidence summary tables (Table 22 and Table 23). Other individual types of documentation are described in 5 studies.[58,135,146,147,153] These are summarised in narrative form in section 9.2.4. See also

the study selection flow chart in Appendix E, forest plots in Appendix J, study evidence tables in Appendix H and exclusion list in Appendix K.

9.2.1 Summary of included studies

Table 19 summarises the main study characteristics of studies investigating the effectiveness of computer systems. Table 20 summarises the main study characteristics of studies investigating the effectiveness of the design of pro-formas and charts. Studies investigating other communication strategies are summarised in Abbreviation: ADR: adverse drug reaction

Table 21.

Table 19: Summary of studies addressing computerised documentation systems

Study	Study design	Documentation type	Outcomes	Comments
Abramson et al. 2011[1]	Prospective non-randomised before–after design	6 providers who adopted e-prescribing within a commercially available electronic health record system and 15 providers who remained paper based	Electronic system users compared to providers not adopting the new system after 1 year: Overall error rates decreased when the new system was brought (from 26% to 16%). Error rates were lower for those providers who adopted new system compared to non-adopters (16% and 38.4%) after 1 year. The main decrease was in 'rule violations' which were departures from the standard prescribing unlikely to cause harm (5.8 in adopters versus 56.5 in non-adopters). Errors labelled 'Near misses' (including allergies) remained stable and did not differ between adopters and non-adopters (1.9% and 2.7%).	The strength of this study was that it provided a comparison group with detailed baseline characteristics.
Bates et al. 1999[9]	Prospective time series analysis with 4 periods	CPOE	Over the 4 time periods medication errors decreased (baseline before adoption of CPOE): 14.2 (before); 5.1 (period 1); 7.4 (period 2); 2.7 (period 3). Included in these errors were documented allergy errors which fell from 10 to 0 over the time period	A large number of medication orders were investigated, for example 14,352 orders alone in Period 3.
Bates et al. 1998[8]	Before-and-after study	CPOE	Mean rate of non-intercepted serious medication errors: Before CPOE: 10.7 events per 1000 patient-days After CPOE: 4.86 events per 1000 patient-days Number of allergy errors: Before CPOE: 0.65 events per	This documentation review has only extracted data from Phase I, and between Phase I and Phase II. The data from post-Phase II were not extracted as there are a number of potential

Study	Study design	Documentation type	Outcomes	Comments
			1000 patient-days After CPOE: 0.29 events per 1000 patient-days	confounders.
Benkhaial et al. 2009[15]	Retrospective data review	ICD-10 codes to be used as part of an electronic drug prescribing system	Proportion of patients with ICD-10 having medication error: 20% Proportion of patients with manual documentation having medication error: 21.6% No difference in the risk of being prescribed a drug potentially inducing an allergy whether the allergy was only documented as an ICD-10 code or documented in the paper record (p=1.0)	The study intended to allocate different drugs and drug groups to ICD-10 codes as guidance for allergy alerts to systemically administered drugs. It assessed the value of the ICD-10 codes as triggers for decision support in an electronic prescription system.
Brown et al. 2000[19]	Indirect comparative study	CPOE / ADE alert system	The screening component of the ADE alert system had a true positive rate of 11% of evaluated alerts, of which 5% were ADEs and 6% were potential ADEs. Total entries into the system: 1643 Entries evaluated by a pharmacist: 759 ADEs documented: 57 ADEs found by traditional methods: 23 ADEs found by the new system: 34 Potential ADEs found by the new system: 48 False positive alerts: 655	The study did not compare the effectiveness of the new ADE alert system with traditional approach using the same set of data. It is not explained in the article how the study obtained the figure of 11% true positive rate. The different categories of counts as shown on the left are not defined clearly in the article.
Colpaert et al. 2006[27]	Non-randomised comparative study	CPOE / Intensive care information system (ICIS)	Total medication prescribing errors (MPEs)*: Computerised unit: 44/1286 (3.4%) Paper-based units: 331/1224 (27.0%) p<0.001 of which: Serious MPEs**: Computerised unit: 23/1286 (1.8%) Paper-based units: 60/1224 (4.9%) p<0.01	Rates of MPEs in 1 computerised unit and 2 paper-based units were compared 10 months after implementation of ICIS in the computerised unit. All medication and fluid prescriptions were checked for errors in a number of recorded elements such as drug name, dosage, route of administration and known allergy to the prescribed drug. The allergy status of the patient was shown by means of a differentially

Study	Study design	Documentation type	Outcomes	Comments
			Total ADEs***: Computerised unit: 2/1286 (0.2%) Paper-based units: 12/1224 (1.0%) p<0.001 In the charts, allergy notation was filled for: 69% of the patients in the computerised unit 2% of the patients in the paper-based units Definitions: *MPE: an error in the prescribing or monitoring of a drug. **Serious MPE: non-intercepted potential adverse drug event (ADE) or ADE. ***ADE: MPE with potential to cause or actually causing patient harm.	coloured highlighted icon in the toolbar as well as in the general prescription window. The main limitations of the study are that the study took place in 1 tertiary care teaching hospital and the type of CPOE implemented is specifically designed for intensive care units, therefore, the findings from the study may not be generalisable.
Evans et al. 1994[44]	Prospective before–after study (Year 1 before introduction of new system, Year 2 and Year 3)	Computer based medical records	Overall Type B adverse drug events (known drug allergies, inappropriate administration and first-time use of drugs) decreased after introduction of the new system. Particularly 'known drug allergies' and 'inappropriate administration' was reduced from 13 to 0 and from 20 to 2 events respectively.	Number of events was very small to start with: 56 in 120,213 patient days at baseline and 18 in 107,868 patient days in Year 3
Evans et al. 1995[42]	Before-and-after study	CPOE: LDS HELP system (LDS Hospital [Salt Lake City, Utah, USA] Health Evaluation through Logical Programming)	Incidence of ADEs due to antibiotics (out of the number of patients receiving antibiotics) Pre-implementation: 15/403 (3.7%) Post-implementation: 3/233 (1.3%) This is a decrease of 2.4%	Computerised logic is used to suggest an antibiotic regimen that would cover the identified and potential pathogens. In addition to infection information, the logic uses patient allergies, drug-drug interactions, toxicity and cost in the selection of suggested antibiotics.
Evans et al. 1998[43]	Prospective cohort study	Computerised management programmes for antibiotic and anti-infective agents	Number of drug allergy alerts Pre-intervention: 146 Post-intervention: 35 Number of adverse events caused by anti-infective agents Pre-intervention: 28	In addition to comparing pre- and post-intervention periods, the authors have also compared between those who had their computer regimen overridden and those who

Study	Study design	Documentation type	Outcomes	Comments
			Post-intervention: 4 Mortality (mean±SD) Pre-intervention: 172±22 Post-intervention (A): 36±18 Post-intervention (B): 52±27	did not, but for some outcomes and not all.
Hsieh et al. 2004[66]	Retrospective data review	Computerised system for drug allergy checking	In total, 80% of the alerts were overridden Only 10% of the overridden allergy alerts were triggered by an exact match between the ordered drug and the listed drugs Reasons given by physicians for overrides were: aware / will monitor (55%); patient does not have this allergy / tolerates (33%); patient taking drug already (10%); other (3%) Rates of different degrees of adverse drug events owing to overridden allergy alerts: fatal (0%); life-threatening (0%); serious (47%); significant (53%)	This chart review was performed on a stratified random subset of all allergy alerts at a large hospital.
Hunte man et al. 2009[69]	Retrospective data review	CPOE	Allergy alerts were triggered at a mean of 2 alerts per patient. Of all the patients whose records were analysed, 47% had a complete allergy profile with information on drug reaction details Of all the drug alerts, 97% were overridden by practitioners. The practitioners' rationales for overriding the alerts were: patient previously tolerated the medication (49%); the benefit outweighed the risk (29%); the medication was therapeutically appropriate (24%); a free-text explanation (8%).	The analysis was carried out only on data from 1 calendar month.
Kuper man et al. 2003[89]	Analysis of design features of 3 different computer systems (descriptive study) of healthcare providers from 1 organisation	CPOE system for drug-allergy checking.	One week's worth of data from 1 of 3 systems was analysed. During this time 1043 drug allergy alerts were overridden 854 could be categorised into the following: Has tolerated in past: 349 (33%) Is aware of allergy: 278 (27%) Will monitor/follow: 159 (15%) Not really allergic: 68 (7%) Other: 189 (18%)	It is unclear what the overall override rate was in 1 week since the total number of orders was not given. Results are only provided as a snapshot rather than real 'study data'.

Study	Study design	Documentation type	Outcomes	Comments
	in Boston (Partners HealthCare)			
Leung et al. 2013[97]	Before-and-after study	CPOE with CDS	Rate of ADEs (per 100 admissions): All ADEs Pre-implementation: 8.9 Post-implementation: 8.3 Preventable Pre-implementation: 8.0 Post-implementation: 4.4 Non-preventable Pre-implementation: 0.9 Post-implementation: 3.9 Rate of potential ADEs (per 100 admissions): All potential ADEs Pre-implementation: 8.9 Post-implementation: 8.3 Intercepted Pre-implementation: 2.1 Post-implementation: 2.9 Non-intercepted Pre-implementation: 53.4 Post-implementation: 133.9	The participants eligible for inclusion were adults with renal failure, exposed to potentially nephrotoxic or renally cleared medications, and admitted to any of the 5 participating hospitals during the study period. The 5 study sites had CPOE systems with variable CDS capabilities: 1) Basic CPOE with no CDS for renal disease (n=2) 2) Rudimentary CDS with laboratory display whenever common renally related drugs were ordered (n=2) 3) The most advanced support where, in addition to basic order entry and lab checks, physicians were provided with suggested doses for renally cleared or nephrotoxic medications, as well as appropriate drug monitoring for medications with narrow therapeutic indices (n=1)
Mahoney et al. 2007[103]	Before-and-after study	CPOE	The number of prescribing errors decreased from 833 before implementation of a Clinical Decision Support System (CDSS) to 109 post-implementation.	The study applied long assessment periods: 1 year before intervention and 1 year after intervention.
Menendez et al. 2012[111]	Before-and-after study	CPOE	Pre-implementation (2004 – 2006): Hand-writing system Post-implementation (2007– 2009): Clinical electronic record Rate of errors: Pre-implementation: 356 errors per 7001 discharges (5.1%) Post-implementation: 1197 errors per 11,347 discharges (10.5%) RR=2.07 (99% CI 1.79 to 2.40)	The study was intended to describe the epidemiology and severity of medication errors detected in an acute geriatric hospital and the impact of the electronic clinical record on reducing these errors.

Study	Study design	Documentation type	Outcomes	Comments
			Rate of moderate to serious errors (E–I)* Pre-implementation: 33 out of 356 all errors (9.3%) Post-implementation: 11 out of 1197 all errors (1%) RR=0.10 (99% CI 0.20 to 0.05) *These categories are from the National Co-ordinating Council for Medication Errors Reporting and Prevention Index for Categorizing Errors (from A to I, in the order of increasing severity).	
Mullett et al. 2001[118]	Before-and-after study	CPOE: anti-infective decision support tool (DST) for a paediatric unit	Impact of introducing the DST was compared between a paediatric intensive care unit and adult shock-trauma intensive care unit (STICU) from a previous study: Impact on drug allergy alerts: Paediatric unit: No change Adult unit: Large reduction Impact on ADEs attributable to anti-infectives: Paediatric unit: No change Adult unit: Large reduction	This paediatric DST was based on a previously studied adult DST. It was designed to account for the therapeutic indication, the age and weight of the patient, the renal function, and the level of prematurity. The frequency of drug allergy was found to be much lower in paediatric patients than in adults.
Neubert et al. 2013[129]	Before-and-after study	CPOE: ADR knowledge base (KB) combined with hospital information systems (HIS)	Pre-implementation: Computerised monitoring system purely on laboratory data with no link to the prescribed medicines or other individual patient data Post-implementation: Use of ADR-KB with HIS combined As a result of the implementation of the new CPOE system, the sensitivity of ADR detection decreased (fewer irrelevant alerts) whilst the specificity increased (more targeted alerts) in 2 departments (internal medicine and paediatrics) in a hospital. Sensitivity: The number of ADR positive patients alerted by at	This study did not analyse drug allergies separately from ADEs, however, it was included for the following 2 reasons: 1) It compares a CPOE with intensive chart review, which is a form of ADE detection strategies that is supposed to be the gold standard. 2) The new CPOE incorporated individual patient data stored in the hospital information system. The researchers wanted to crosslink a standard CPOE with individual patient data so that the signals generated are highly specific to that

Study	Study design	Documentation type	Outcomes	Comments
			least 1 signal in relation to the total number of ADR positive patients Specificity: The number of all non-ADR patients not alerted by any signal in relation to the total number of non-ADR patients.	patient.
Soto et al. 2002[155]	Retrospective review of electronic records from 834 patients receiving care from 167 physicians	Electronic medical records	Completion of drug allergy medical record documentation was low: 61.6% completion rate for internists and 50.4% for paediatricians	The main aim was to assess whether the documentation rate depended on physician specialty rather than documentation strategy.
Spina et al. 2011[156]	Cross-sectional national survey (total respondents n=1543)	Experience with electronic prescribing system	42% of respondents rely on the computer system to alert them about patient medication allergies. 81% reported that they enter a serious reaction into the appropriate data field and 15% that they would inform a pharmacist.	This study relied on self-reported survey answers rather than direct checks.
Tambly n et al. 2008[159]	Randomised controlled trial	Computer-triggered alert system (automatic) compared to on-demand (can be accessed during the prescribing process) drug management systems	1% (41/4445) of prescribing problems were seen by physicians using on-demand compared to 10% (668/6505) of computer triggered. However of those seen 76% (31/41) were acted on by on-demand group and 12% (81/668) in the computer triggered group. Main reasons for overrides were 'benefit greater than risk' and 'interaction already known' or 'not clinically important'.	Even though the study quality is higher than those of other studies, it is unclear how many of the prescribing problems directly refer to drug allergies.
Varkey et al. 2008[165]	Retrospective survey	CPOE	Frequency of intercepted prescription errors: Handwritten prescriptions: 7.4% Computerised prescriptions: 4.9% Pre-printed prescriptions: 1.7%	The authors applied systematic random sampling, and reviewed prescriptions ordered each March of 1996, 1998, 2000 and 2002.

Abbreviations: ADE: adverse drug event; ADR: adverse drug reaction; CDS: clinical decision support; CPOE: computerised physician order entry system; DST: decision support tool; ICD: International Classification of Diseases; MPE: medication prescribing error; SD: standard deviation

Table 20: Summary of studies addressing design of pro formas and charts

Study	Study design	Documentation type	Outcomes	Comments
Coombes et al.	Prospective before-and-	Standardised revised	All prescribing errors: Pre-implementation: 23.5%	The focus of this study is on ADR documentation

Study	Study design	Documentation type	Outcomes	Comments
2009[29]	after observational audit	medication chart	Post-implementation: 18.7% Number of patients with ADRs and the incidence of ADRs: Pre-implementation: 25.3% (302 ADRs) Post-implementation: 26.2% (311 ADRs)	alerts and warfarin management, not on allergies.
Eneh & Fahy 2011[41]	Before–after audit in 6 psychiatric wards (2 acute and 4 long stay)	Formal assessment pro forma with clearly designed allergy section based on results from the first audit	After introduction of the new pro forma compliance with documentation of allergy status increased particularly in medication charts and admission notes, but less so on the front of case notes.	It was stated that 'renewed awareness of the importance of documentation of allergy status was created', that is, results cannot be only attributed to the design of the pro forma.
Harris et al. 2002[60]	Randomised controlled trial	Structured pro forma for GP–emergency department communication	Number of referral letters that GPs sent out: Intervention: 307 Control: 225 Number of times 'allergies' was included in the referral letters: Intervention: 55 (18%) Control: 4 (2%)	This is an RCT. The form is specifically for communication between GPs and emergency departments.
Hippern et al. 2000[62]	Prospective patient interview and retrospective review of existing records	Structured penicillin allergy assessment form	A pharmacist interviewed patients with suspected allergy to penicillin using the intervention (structured penicillin allergy assessment form) and found that: 18/60 (30%) had a probable true allergy 32/60 (53% had a possible true allergy 8/60 (13%) had a side effect or intolerance 2/60 (3%) were unlikely to have allergy	It assessed the validity of the allergy data in the existing unstructured method of recording penicillin allergy using an interviewer-led structured assessment form.
Marco et al. 2003[105]	Retrospective data review	Revised form of a new anaesthesiology preoperative evaluation form	Number of times allergy component was present in the forms: Older form: 111/112 (99%) Newer form: 102/105 (97%)	It is indicated that this retrospective review was 'randomised' but this concept has not been explained in the main text.
Mead et al. 1999[110]	Prospective review of referral letters	Pro formas compared to unstructured letters	Quality of 300 referrals was assessed according to presence of the following categories (demographic details; current, past and social history, drugs and allergies): No overall difference in quality between pro forma or	People who rated the letters did not show strong agreement in their assessment of quality (Kappa values ranged from 0.26 to 0.44)

Study	Study design	Documentation type	Outcomes	Comments
			unstructured referrals Only 16% of referrals included information on allergies	
Simmonds et al. 2000[152]	Retrospective data review followed by a before-and-after study	New preoperative assessment sheet	Frequency of recording of allergy by anaesthetists: Pre-intervention: 79/195 (40.5%) Post-intervention: 75/227 (33.0%)	Allergy was only 1 of 12 elements that the study assessed.
Ortega et al. 2008[132]	Retrospective data review followed by a before-and-after study	ADR computerised reporting tool integrated into the hospital information system for national drug surveillance system	As a result of the 5 improvement measures implemented, there was a reduction in all of the following: Suspected allergy Studied allergy Yellow Cards sent Yellow Cards necessary	The duration of Phase I was 29 months and that of Phase II was 8 months. In terms of the length of period and the quantity of data obtained, it is not a fair comparison.
Zenk et al. 1984[175]	Before-and-after study	Chart card with designated boxes to enter allergies and weight	Completion rate of allergy information at baseline were 33.3%, during the intervention 74% and post-intervention (without the intervention) it was 47.3%	Even though special training was provided, completion rate went down again once the structured form was withdrawn suggesting that the effect originated from the form rather than the training.

Abbreviation: ADR: adverse drug reaction

Table 21: Summary of studies reporting other documentation strategies

Study	Study design	Documentation type	Outcomes	Comments
Hackl et al. 2013[58]	Controlled interrupted time series analysis, qualitative interviews and standardised survey	ADE scorecards	Rate of detected ADE* cases (per 1000 inpatient stays) 15 months pre-implementation 15 months post-implementation Departments that received the intervention: (Intervention groups, n=3) Pre-implementation: 812 Post-implementation: 706 Decrease of 106 cases per 1000 inpatient stays Departments that did not receive the intervention: (Control groups, n=2) Pre-implementation: 99	The regression analysis comparing the pre-implementation and post-implementation periods in each department and comparing intervention departments and control departments, taking into account baseline ADE trends in all departments, showed no significant changes in ADE rates after the introduction of the ADE scorecards. All 13 of the interviewed healthcare professionals considered the ADE scorecards to be useful to support decision-making and they expressed their

Study	Study design	Documentation type	Outcomes	Comments
			Post-implementation: 109 Increase of 10 cases per 1000 inpatient stays *Definition of ADE used: "Any injury occurring during the patient's drug therapy and resulting either from appropriate care, or from unsuitable or suboptimal care."	intention to use the ADE scorecards as part of an ADE prevention approach. In the survey conducted after 1 year of use, all respondents stated that they would recommend using the ADE scorecards to their colleagues. Except for 1 physician, all healthcare professionals were convinced that ADE scorecards could contribute to increased medication safety.
Porter et al. 2006[135]	Observational study at triage in paediatric ED setting	Review of medication orders and presence of allergy bracelet on the child	Of 28 children assessed to have an allergy 16 (57%) wore a bracelet. 5 of the children who had a bracelet, details did not agree with the assessed allergy (2 with false positive information and 3 blank). 111 children had at least 1 medication ordered and for 5 children with allergies the medication order was documented as negative. No cases of medication error were noted.	The main focus of the study was on accuracy of documentation rather than documentation as an intervention strategy.
Sard et al. 2008[146]	Retrospective before and after comparison	'Quicklist' (a list of medication commonly prescribed in a paediatric hospital) added to the CPOE	Errors per 100 orders decreased from 31 to 14. With respect to drug allergies errors per 100 orders decreased from 2 to 0.	The aim of the study was to reduce overall error rate. Therefore little detail is provided about the computer system's ability to alert to allergies.
Schadow et al. 2009[147]	Non-randomised comparative study	Structured Product Labelling (SPL) drug knowledge representation added to CPOE	The study concluded that although less than 70% of the terms were mapped to SPL, it detected 4 times as many drug intolerance issues on twice as many patients. However, on closer inspection, the figures for allergies indicate that there was no difference between the intervention (SPL+CPOE) and the control (existing CPOE system) in terms of detection of allergens.	The comparator of this study was an in-house CPOE decision support system and thus it may not be applicable to other widely used CPOE systems.
Soller et al. 2012[153]	Non-randomised comparative study	Revised over-the-counter ibuprofen allergy alert	Overall preference of allergy-naïve consumers: Existing alert: 22% Revised alert: 78% Overall preference of drug-	There was a financial incentive for the 'naïve consumers' to participate in this study.

Study	Study design	Documentation type	Outcomes	Comments
			induced allergy survivors: Existing alert: 0% Revised alert: 100%	

Abbreviations: ADE: adverse drug event; CPOE: computerised physician order entry system; SPL: structured product labelling

9.2.2 Computerised prescribing systems

Table 22: Clinical evidence summary table: computerised prescribing systems

Number of studies	Study designs	Type of electronic system	Rate of errors at baseline	Effectiveness of systems – error rates	Effectiveness of systems – prevention of allergic reactions	Overrides	Reasons for overrides	Quality(a)
21	1 RCT 1 prospective cohort study 1 indirect comparative study 10 before-and-after design studies 4 retrospective reviews 2 surveys 1 descriptive analysis study	Computerised physician order entry systems Electronic medical record systems Adverse drug event alert systems Systems using ICD-10 codes Drug checking systems ADR reporting tools	Error rates were given in different units. Per overall order errors (converted to 100 orders) range: 14–24% By patient days: 0.04–1.1 Proportion of patients: 20–25%	Before–after studies showed a decrease in error rates: Per order: ~10% Per patient days: 0.03–0.5 One described total number reduction only: from 833 to 109 2 direct comparisons showed e-prescribing no more effective than hand written orders	The rate of 'near misses' did not differ significantly between a CPOE and paper system (1.9 versus 2.7 per 100 orders) Number of non-intercepted potential adverse drug events (ADEs) as well as preventable ADEs decreased from 5.89 to 1.16 and 4.50 to 3.65 respectively Preventable and non-intercepted serious medication errors were described to decrease after implementation from 2.9 per 100 patient days to 1.1 and 7.6 to 1.1 respectively Adverse events caused by anti-infective agents decreased from 28 to 4 after implementation Rates of adverse drug events owing to overridden allergy alerts was 5.9 per 100 patients (3.1 significant and 2.8 serious) After implementation the number of suspected and detected ('studied') allergies went down from 90 to 24 and 15 to 5 respectively	69–97%	Patient tolerated in the past Patient is already taking the drug Benefits outweigh harms Patient aware and will be monitored Not really allergic	VERY LOW

(a) The majority of evidence stems from study designs with major risks of bias, such as retrospective and before–after designs. The method of analysis was also often not adequately described and did not adjust for any differences in group characteristics.

Narrative summary of other findings relating to computerised prescribing systems:

- In 1 study,[132] a national survey, 42% of responding physicians reported that they relied on the computer system to alert them to the drug allergy.
- Another study[155] reported overall low completion rates of drug allergy records (61.6 for internists and 50.4 for paediatricians).
- In the randomised controlled trial[159] physicians using an on-demand system noticed fewer errors, but acted on the majority of those that they looked at (saw 1% and acted on 76% of those seen). Physicians using an automatic system saw more of the prescribing problems but only acted on a minority of those seen (saw 10% and acted on 12% of those seen).
- One study[97] found that change in ADE rate depended on the level of Clinical Decision Support System (CDS). Computerised Prescriber Order Entry system (CPOEs) with the more advanced CDS features resulted in more significant reduction of Adverse Drug Events (ADE).
- Introduction of CPOE in 1 study[111] led to increase in the overall number of medication errors but decrease in the number of serious errors.
- Incorporation of individual patient data in to an existing computable ADR knowledge base in 1 study[129] led to decrease in sensitivity but increase in specificity of the ADR detection system.
- In general, CPOEs evaluated in more recent years tended to be adapted to suit the purpose of the study site.

9.2.3 Pro formas or structured charts

Table 23: Clinical evidence summary table: pro formas or structured charts

Number of studies	Study designs	Pro forma types	Features of new pro forma	Effectiveness of new pro forma	Effectiveness-prevention of allergic reactions	Quality[(a)]
9	1 RCT 5 studies with before-and-after study components 1 retrospective data review with prospective patient interview 2 prospective	2 studies assessed a preoperative assessment form for patients undergoing surgical procedures 1 study assessed a standardised medication chart for inpatients 2 studies assessed a formal assessment pro forma with a clearly designated allergy section for i) use in paediatric inpatient unit and ii) within a department of psychiatry. 1 study assessed a structured	Making patient info more visible Giving prompts for clinicians to provide certain info, including allergy Allowing clinicians to provide detailed history of previous reactions Clearly designating an allergy-only section For communication	Positive outcomes observed Reduction in prescribing errors Increase in compliance with documentation of allergy status in some charts but not others Increase in referral letters that include allergy information Increase in accuracy of allergy identification Increase in the number of times allergy components were included/completed	One study reported the changes in rates of reactions: It was described that drug selection (previous ADR) was reduced from 21/9772 (0.21%) to 9/10352 (0.08%)	VERY LOW

Number of studies	Study designs	Pro forma types	Features of new pro forma	Effectiveness of new pro forma	Effectiveness-prevention of allergic reactions	Quality[(a)]
	review of referral letters and admission records	penicillin allergy assessment form for patients attending a day surgery unit at a hospital 1 study assessed a structured pro forma for communication between GP practices and emergency departments	between GPs and EDs: the front side was for GPs and the reverse side was for EDs to provide outcomes of the referred case Standardised to be consistent with other forms used in local area	Negative outcomes observed Increase in adverse drug reactions No overall difference in quality of information between new pro forma or previous version Decrease in frequency of recording of allergy by anaesthetists		

(a) The majority of evidence stems from study designs with major risks of bias, such as retrospective and before–after designs. The method of analysis was also often not adequately described and did not adjust for any differences in group characteristics.

9.2.4 Other documentation strategies

- One study[146] integrated a 'quicklist' containing the 75 most commonly prescribed medications in a paediatric department to the computerised order system and compared this to a computerised system without this list (that is, before implementation). Errors per 100 orders decreased from 31 to 14. With respect to drug allergies, errors per 100 orders decreased from 2 to 0. (Very Low quality evidence)
- One study[135] in an US paediatric emergency department reported that out of the 28 children with confirmed drug allergy, 16 (57%) were given a bracelet. 5/16 (31%) were incorrect or blank. (Very Low quality evidence)
- The addition of structured product labelling to a computer system was investigated in another study.[147] Even though the authors concluded that the structured system detected 4 times as many drug intolerance issues in twice as many patients, closer inspection of the results do not show differences in the detection of allergens between the intervention system and the existing system. (Very Low quality evidence)
- Results from a study of a revised version of an over-the-counter ibuprofen allergy alert, which included more information on symptoms of drug allergies, indicated that 78% of consumers and 100% of people with previous drug allergies preferred the revised version. (Very Low quality evidence)
- In 1 study[58], introduction of ADE scorecards, a tool aimed to increase team ADE awareness by allowing information on ADE available to the entire care team, did not lead to any significant change in the rate of ADE. (Very Low quality evidence)

9.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

9.4 Evidence statements

Clinical

Computerised medical records and prescriptions

- Very low quality evidence from 20 observational studies and 1 RCT showed that error rates tended to decrease after computer systems were introduced. Some studies did not show an overall improvement when direct comparisons were made between paper-based and computer-based prescriptions. In the studies reporting on overrides the majority of computer alerts (69–97%) were ignored. One observational study demonstrated that the resulting changes in adverse drug event (ADE) rates depended on the complexity of clinical decision support (CDS) incorporated in the host CPOE: the more advanced the CDS was the lower the ADE rates following introduction of the CPOE.

Pro formas or structured charts

- Very low quality evidence from 6 observational studies and 1 RCT evaluated new or revised versions of structured forms which allow the clinicians to record patient history and other clinical factors, and to assess patients' allergy status. Some of the positive outcomes included: increase in compliance with documentation of allergy status, presence of allergy information in referral letters, accuracy of allergy identification, the number of times allergy components were included or completed, and reduction in prescribing errors. Some of the negative outcomes were: increase in adverse drug reactions (in 1 study), decrease in frequency of recording of allergy by anaesthetists and no overall difference in quality of information provided by clinicians following intervention.

Other strategies

- Very low quality evidence from 5 observational studies showed that i) the medication error rate decreased following an integration of a 'quicklist' to an existing computerised system; ii) drug allergy information on a significant proportion of children's bracelet were incorrect; iii) structured product labelling did not have a significant impact on allergen detection; iv) a revised, more comprehensive version of an over-the-counter ibuprofen allergy alert was preferred; and v) introduction of ADE scorecards did not lead to change in ADE rate.

Economic

- No relevant economic evaluations were identified.

9.5 Recommendations and link to evidence

Recommendations	Documenting and sharing information with other healthcare professionals Recording drug allergy status

8. **Document people's drug allergy status in their medical records using 1 of the following:**
   - **'drug allergy'**
   - **'none known'**
   - **'unable to ascertain' (document it as soon as the information is available).**

9. **If drug allergy status has been documented, record all of the following at a minimum:**
   - **the drug name**
   - **the signs, symptoms and severity of the reaction (see recommendation 1)**
   - **the date when the reaction occurred.**

Documenting new suspected drug allergic reactions

10. **When a person presents with suspected drug allergy, document their reaction in a structured approach that includes:**
    - **the generic and proprietary name of the drug or drugs suspected to have caused the reaction, including the strength and formulation**
    - **a description of the reaction (see recommendation 1)**
    - **the indication for the drug being taken (if there is no clinical diagnosis, describe the illness)**
    - **the date and time of the reaction**
    - **the number of doses taken or number of days on the drug before onset of the reaction**
    - **the route of administration**
    - **which drugs or drug classes to avoid in future.**

Maintaining and sharing drug allergy information

11. **Prescriptions (paper or electronic) issued in any healthcare setting should be standardised and redesigned to record information on which drugs or drug classes to avoid to reduce the risk of drug allergy.**

12. **Ensure that drug allergy status is documented separately from adverse drug reactions and that it is clearly visible to all healthcare professionals who are prescribing drugs.**

13. **Check a person's drug allergy status and confirm it with them (or their family members or carers as appropriate) before prescribing, dispensing or administering any drug (see also recommendation 20). Update the person's medical records or inform their GP if there is a change in drug allergy status.**

14. **Ensure that information about drug allergy status is updated and included in all:**

	• **GP referral letters** • **hospital discharge letters** **15. Carry out medicines reconciliation for people admitted to hospital in line with recommendations in Technical patient safety solutions for medicines reconciliation on admission of adults to hospital (NICE patient safety solutions guidance 1).** **Documenting information after specialist drug allergy investigations** **For recommendations on referral to specialist services see Chapter 12** **16. After specialist drug allergy investigations, allergy specialists should document:** • **the diagnosis, drug name and whether the person had an allergic or non-allergic reaction** • **the investigations used to confirm or exclude the diagnosis** • **drugs or drug classes to avoid in future.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: medication errors (inappropriate prescription or administration of drugs), number of repeat drug allergic reactions, inappropriate avoidance of drugs and quality of life. The first 2 were considered by the GDG to be the most important outcomes. Not all of the stated outcomes were found in the studies included. In general, most of the studies reported outcomes related to medication prescribing errors or adverse drug reactions, and not specifically to drug allergy.
Trade-off between clinical benefits and harms	The GDG noted a recent report by NHS England [130] which highlighted the high incidence of medication errors and agreed that errors in prescribing and administering drugs are a serious concern. The GDG observed that, at present, the labelling and coding used in electronic documentation systems do not enable such systems to differentiate between a side effect and an allergic reaction. It was agreed that if the information entered into such systems was of poor quality in the first instance then the output would also be of poor quality. The GDG considered that any system which allows accurate recording of information and prevention of erroneous prescription or administration of medications would be highly beneficial in improving patient safety. Studies related to computerised prescriber order entry (CPOE) systems showed very high rates of overriding of automated alerts (between 69% and 97%). The GDG indicated that once a patient has been diagnosed as having a drug allergy, this status would remain on the patient's record. Therefore, if a patient had previously been incorrectly diagnosed as having a drug allergy, the trigger alerts at subsequent visits to their physician would be overridden. Those studies that implemented a structured approach to documentation saw a reduction in medication prescribing errors and adverse drug reactions, and also an increase in healthcare professionals' compliance in completing patients' medical charts. The GDG therefore endorsed the application of structured documentation to record details of suspected drug allergies.
Economic considerations	No relevant economic evidence was identified. The GDG did not prioritise this question for original economic analysis. The GDG agreed that accurately documenting a person's current drug allergy status is vital in order to prevent inadvertent exposure to an allergen, and so to ensure

	patient safety. Whilst this may require an initial increase in healthcare professionals' time whilst current records are improved, in many cases this is likely only to bring forward a discussion that a GP will have with the person at some later point in time. The GDG were confident that any cost from increased numbers of GP consultations would be outweighed by increases in quality of life and costs saved due to future additional drug allergic reactions avoided. Similarly, accurate documentation of all new suspected allergic reactions to drugs will help identify appropriate future treatment, leading to better clinical outcomes and improved quality of life, at low cost. Documentation of reactions which are found not to be allergic reactions will reduce the unnecessary future avoidance of drugs and so reduce the usage of more expensive and potentially less effective alternatives. Accurate and sufficiently detailed recording of information regarding reactions at the time they are first reported will also reduce time spent later attempting to understand records relating to drug allergy which are unclear or unstructured. As noted above, there is a significant incidence of medication errors at the point of drug prescription and administration.[130] Avoidable repeat reactions can have significant impact on the health and quality of life of people who experience them and will give rise to significant treatment costs; low cost methods of reducing these errors are therefore likely to be cost effective. Checking the drug allergy status of a person before prescribing them a drug would take a matter of seconds within the course of a normal GP consultation for a person whose status has already been systematically documented according to these recommendations and whose status is unchanged. In the same way, the GDG agreed it would take healthcare professionals who dispense and administer medication a few seconds more to read prescriptions including slightly more information and to confirm this with the patient. Although a short amount of additional time added to many thousands of GP consultations and occasions when drugs are administered could add up to a significant total, the GDG emphasised the importance of accurate documentation and information sharing between health services in reducing both avoidable repeat allergic reactions and the costs involved in treating those reactions. There is also a possibility that time would be saved in some cases where a patient is currently asked to explain their full allergy history on multiple occasions to those prescribing, dispensing or administering drugs who are currently not provided with sufficient allergy information, and so need to elicit the information afresh on each occasion. The GDG agreed that these strategies were therefore likely to be highly cost effective compared to current practice.
Quality of evidence	The studies included were predominantly observational studies from the USA and the electronic systems that they evaluated were designed and developed to suit the purpose of the study site. None of these systems can be directly compared with current or prospective systems in the UK. Importantly, most of the studies focused on rates of medication prescribing errors or adverse drug reactions in general, and data specific to drug allergy were minimal. The outcomes of the included studies varied considerably, with some documentation strategies leading to positive results whilst others led to less favourable effects. Positive findings from the implementation of computerised systems cannot necessarily be attributed to the system alone. It is possible that introduction of a new system itself raises awareness amongst the personnel working at the site, or that training that accompanies the system's introduction improves practice amongst healthcare professionals. The studies did not provide sufficient data on what training was provided with the computerised systems. Overall, although the studies observed a reduction in medication prescribing errors and adverse drug reactions, the evidence from these studies was varied and of very low quality. Therefore, the evidence did not enable the GDG to make

	recommendations on specific systems, and highlighted the need for further research.
Other considerations	The GDG noted that there is an increase in the use of computerised systems and a push towards paperless systems being introduced in the NHS . However, in the absence of evidence, it is not possible to make recommendations specifically for computerised systems. Nevertheless, the GDG recognised that the quality of the information recorded within any documentation system is paramount and concluded that having a well organised, structured system in any format would be very helpful in reducing the number of prescribing errors and preventing allergic reactions. Specifying the information that needs to be recorded and allocating specific locations for details of drug allergy to be recorded will serve to enhance the skills of healthcare professionals in taking medical histories and increase their compliance in completing patients' medication charts. Details on the type of information or the level of detail being documented in patient records were not described within the studies. The GDG drafted consensus recommendations on when drug allergy status should be recorded, the level of detail required and who this information should be shared with based on their own clinical experience, and recent publications that have highlighted areas of good practice.[2] The GDG was aware that some hospitals already have prescription forms including drug allergy status, but that this was not currently part of GP or dentist standard prescription forms (FP10, HS21B). The group noted the current inequality this posed in the delivery of care between primary and secondary settings. Given the GDG's observation on the lack of communication between healthcare professionals in primary and secondary care and across different departments within hospitals, it is important to ensure that structured documentation is in place at all levels of patient care. The GDG agreed that most prescriptions are now generated electronically and therefore including information on a patient's drug allergy status is possible.. It was noted that community pharmacy has a role in minimising re-exposure to drugs where there is a known drug allergy, and having information on the prescription form would enable this and help improve patient safety. The GDG agreed that a review of systems, including prescription forms for recording drug allergy is required because current levels and methods of documentation are inadequate. To prevent the loss of information about a patient's drug allergy between contacts with healthcare providers, it is important that patients are given the necessary information and details of their own drug allergy status, and that such information is held by the patient and shared with their clinicians. Evidence and recommendations related to this issue can be found in Chapter 10 (Information and support). Guidance on medicines reconciliation on hospital admissions is available in NICE patient safety guidance 1 (PSG1). The guidance aims to lay out patient safety solutions to ensure that medicines prescribed on admission correspond to those that the patient was taking before admission. The GDG also noted the recent i-care report[2] of the Academy of Medical Royal Colleges that highlighted the need for patient records to follow a standardised structure and content and to be available across organisational boundaries. The report's recommendation for a recognised nomenclature of clinical terms such as SNOMED to be used within the NHS was endorsed by the GDG. Computerised systems for patient records currently use a variety of different codes for drug allergy, and the GDG agreed implementation of a standard code and terminology would improve patient safety and management.

10 Providing information and support to patients

Patients are often left bewildered following a suspected allergic reaction to a drug. Many questions are asked and too often few are answered: Was the reaction predictable? Should I have been prescribed the drug? Will I have a more severe reaction next time? Which drugs do I need to avoid? Am I at risk when taking a new drug in future? How will this impact on my future treatment?

Fear of experiencing a further reaction can be heightened by a lack of information and worsened if the original reaction was severe. If the patient's record of the details of the allergic reaction is incomplete or the patient is not provided with written information, then the patient may either remain at risk of inappropriately receiving the same or a cross-reacting drug again, sometimes with catastrophic consequences, or a different drug may be incorrectly and unnecessarily avoided in the future, compromising the quality of future medical treatment. A drug allergy may not have been responsible for the original reaction, and so if drug allergy is excluded it is equally important that this information is conveyed to the individual in order to provide reassurance and enable optimal treatment to be prescribed in future.

Written information given to the patient at the time of the reaction, with details of drug, number of doses and the nature and severity of the reaction will avoid uncertainty and in many cases allow prescription of an alternative drug not known to cross-react with the original compound. Details of the drug and reaction are invaluable if the same drug is needed again and will also increase the accuracy of diagnosis if the patient requires referral for specialist drug allergy investigation.

10.1 Review question 1: What information and support should individuals with suspected drug allergy or their parents and carers receive?

10.2 Review question 2: What information and support should individuals who have had specialist investigations or their parents and carers receive?

Table 24: Summary of protocol characteristics of review question

Population	Patients (or their family and carers) with history or experience of suspected or diagnosed drug allergy
Intervention	Information about diagnosis and management of drug allergy
Comparison	Information strategies compared with each other
Evaluation themes	Patient experiences; preferences; perceptions, including factors which improve or act as a barrier to optimal care. Clinical and quality of life outcomes related to diagnosis and management of drug allergy.
Study design	Qualitative studies and surveys

A single search was conducted for the 2 review questions relating to patient information. The studies identified are presented in a single review, as the information was applicable to both questions.

Qualitative studies were identified as the main source of evidence for this review. The analysis of qualitative studies involves a search for common themes in participants' discourse. The themes from each study were extracted and it was then investigated how many studies identified the same theme or different themes. This evidence is summarised in Table 26.

For full details see the review protocol in Appendix C and study selection flow chart in Appendix E.

10.3 Clinical evidence

Eight qualitative studies were identified.[6,21,22,50,68,88,90,101] Studies which addressed adverse drug reactions were included if they discussed patients with drug allergies as a subgroup of the study population. Of the 8 studies, 1[6] directly applies to children; all other studies refer to adults with drug allergies. Summaries of study characteristics are presented in Table 25. In Table 26 common and individual themes are identified and summarised. Study quality is assessed according to criteria specific to qualitative research methods. These include clearly specified aims, study design, data collection and rigour of analysis. The complete list of quality characteristics is provided in the footnote to Table 25.

10.3.1 Study summary and quality

In Table 25 the included studies are briefly described. See Appendix H for full details of the studies. The numbers in the quality characteristics column refer to those characteristics, from a list of 14 items, which were assessed to be adequate or good.

Table 25: Summary of studies included in the review: study quality

Reference	Population and setting	Aims of study	Data collection	Quality characteristics[(a)]	Confidence in study
Arnott et al. 2012[6]	Parents of 44 children with suspected adverse drug reactions; Edinburgh	To inform the management of communication about ADRs in children and to identify any unmet psychological, information and communication needs described by parents.	Semi-structured interviews	1, 2, 3, 4, 5, 8, 9, 11, 12, 13, 14	Moderate
Butt et al. 2011[21]	14 adult survivors of SJS and TEN; 2 hospitals in UK	To explore the experiences, beliefs and attitudes of survivors of serious ADRs, using drug-induced Stevens–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) as a paradigm.	Retrospective qualitative study using detailed semi structured interviews	1, 2, 3, 4, 5, 9, 12, 13, 14	Moderate
Butt et al. 2012[22]	Adult survivors of SJS and TEN; 208 internet descriptions	To interpret the reasons for individuals with serious ADRs posting information about their experiences on	First person written narratives by patients, relatives or friends. 139 descriptions were posted	1, 2, 3, 4, 5, 8, 9, 12, 13, 14	Moderate

Reference	Population and setting	Aims of study	Data collection	Quality characteristics[(a)]	Confidence in study
		the internet to determine whether issues discussed by patients and their relatives in their internet descriptions differ from those found through interviewing survivors of the condition face-to-face.	by patients, 69 by relatives and 1 was jointly submitted by patient and relative. Of those posted by relatives, 30 were posted by mothers.		
Franic & Pathak 2000[50]	Random sample of 400 female patients of child bearing age from the Women's Clinic at the Ohio State University Medical Center in Columbus, Ohio, USA. 74 of the returned surveys were useable.	There were 6 objectives over all, 1 of which was relevant to this review: Do study participants prefer numerical as opposed to verbal descriptors in the communication of ADRs as drug therapy? (that is, not only what information should be communicated but how should it be presented)	Cross-sectional field study using survey instruments	1, 2, 3, 4, 5, 7, 8, 10, 12, 13, 14	Moderate
Hughes et al. 2002[68]	10 adult patients purchasing a selected medicine (antihistamine, decongestant or ibuprofen) at a community pharmacy were interviewed. 4 focus groups of 22 patients total recruited through 2 local schools.	To investigate the knowledge of patients with regard to the side effects of over-the-counter medicines and the source of this information.	Ethnographic interviews and focus groups in Welsh School of Pharmacy, Cardiff University, UK	1, 2, 3, 4, 5, 13, 14	Low
Krska et al. 2011[88]	1362 questionnaires, 27 telephone interviews and data from 230 Yellow Card reports all collected in the UK.	The aim was to determine how reporters to the Yellow Card Scheme identify	A qualitative analysis from 3 sources was carried out: responses to	1, 2, 3, 4, 5, 8, 11, 13, 14	Moderate

Reference	Population and setting	Aims of study	Data collection	Quality characteristics[(a)]	Confidence in study
		adverse drug reactions.	open questions in postal questionnaires sent to all reporters during March 2008–January 2009 were categorised by 2 researchers independently; telephone interviews with a purposive sample of these reporters and the free-text field from completed Yellow Card reporting forms submitted during October 2005–September 2007.		
Laaksonen et al. 2002[90]	82 patients were recruited using convenience sampling at a London teaching hospital during autumn 2000. 15% were assessed as having 'definite' or 'probable' adverse drug effects based on the Naranjo algorithm. The extent of information the patients desired was assessed through the 'extent of information desired' (EID) scale, a subscale of a larger 12 item scale that assesses the 'Intrinsic Desire for Information' (IDI scale).	The aim was to explore the characteristics of medical patients, their information requirements, relationships with their perceptions about prescribed medicines and coexistent adverse drug effects.	Semi-structured questions explored patients' perceptions of the adverse effects of prescribed drugs.	1, 2, 3, 4, 5, 6,8, 9, 11, 13, 14	Moderate
Lorimer et al. 2012[101]	Patients with severe ADR admitted to a hospital for severe drug reactions 7 out of 15 had allergic	To explore patients' experiences of severe ADR and	Semi-structured interview template was	1, 2, 3, 4, 5, 8, 9, 11, 12, 13, 14	Moderate

Reference	Population and setting	Aims of study	Data collection	Quality characteristics[(a)]	Confidence in study
	reactions, including angioedema (enalapril (1), enoxaparin (1), clarithromycin (1)), Stevens–Johnsons syndrome (sulfasalazine (1)), severe rash (penicillin (1)), severe urticaria (amoxicillin (1)), allergic reaction to contrast media (1). Other reactions were gastrointestinal bleeds (NSAIDS (3)), extrapyramidal effects (metoclopramide (1)), jaundice (cimetidine (1)) urinary retention (antipsychotics (1)) bruising due to interaction with warfarin (clarithromycin (1)), muscle weakness, headache and confusion (statins (1)).	their views on reporting their ADRs to the Yellow Card scheme.	used. Open questions were used to explore the patients' views of their suspected ADR, information they have received about their medication, the potential effect on their future medication use and their views and knowledge of the Yellow Card scheme.		

(a) Quality characteristics assessed:

1. Clear aims
2. Adequate background
3. Appropriate methodology
4. Appropriate design
5. Appropriate recruitment strategy (sample and sampling) and appropriate data collection
6. Reliability of data collection tool
7. Validity of data collection tool
8. Data collection methods described adequately
9. Data analysis methods described adequately
10. Reflexivity
11. Ethical issues
12. Rigorous data analysis
13. Clear findings
14. Value of research

10.3.2 Summary of themes

All themes identified by the authors of the included studies were extracted. Adverse drug reactions were not always separated from the subset 'drug allergy' but were included if the theme could be extrapolated to allergy. Nine themes are summarised in Table 26 below.

Table 26: Summary of themes and related studies

Qualitative theme	Points highlighted in the theme	Studies identifying this theme
Poor explanations of possible adverse	Clinicians focused on other issues	Arnott 2012; Butt 2012

Qualitative theme	Points highlighted in the theme	Studies identifying this theme
events or side effects of medications	Written information not given or difficult to understand	
Non-medical sources of information	Personal experience with medicines Media coverage Information from family and friends Seeking advice of others with similar experience about cause, symptoms and treatment Internet (possible source of anxiety) Books Patient information literature not universally read. Reasons for reading: if medicine was new or not a regular medicine; side effect was experienced; medicine was for a child	Arnott 2012; Butt 2012; Hughes 2002; Krska 2011
Management and communication with regards to ADR	Information poorly matched to parents' need at a time of fear and anxiety Contradictory information Concerns ignored or dismissed	Arnott 2012
Implications of poor communication for patients and carers	Lack of information limits parental involvement about decisions for their child Fear of repetition of ADR Withholding of medications; avoidance of medicine in general Fear of effect on reproduction (fertility, heredity) Fear that other medical conditions may be related Less trust in healthcare professionals	Arnott 2012; Butt 2011; Butt 2012;
Feelings about the experience of having an ADR	Disbelief Anger Fear of future reaction; fear of losing a useful therapeutic option Frustration Isolation	Lorimer 2012
Information needs	Discussion with clinician of what happened Implications for future health How to avoid future reaction Patients who have had an adverse drug reaction are more interested in receiving information than those who have not had a reaction	Arnott 2012; Laaksonen 2002
Communication skills	Dialogue with clinician; information seen as responsibility of medical staff Internet web sites and chat groups Accessible and reliable information from pharmacist (rather than the Internet) Support from the stories of others Support from patient groups Information about side effects or risks most helpful if provided numerically	Arnott 2012; Butt 2011; Butt 2012; Franic 2000
Linking signs and symptoms to possible ADR	Timing of reaction Reaction listed in the patient information literature received Symptom was unusual or never had it before	Hughes 2002; Krska 2011

Qualitative theme	Points highlighted in the theme	Studies identifying this theme
	Changes with dose and rechallenge	
Problems with patient information literature	Writing too small Information related to children's medication dosage confusing and should be related to height and weight Long lists of side effects would cause patients to wrongly attribute symptoms to their medication Underused: Hughes et al. 2002, only 3/32 patients had read the patient information literature; Lorimer et al. 2012 not patients' job to inform themselves but the doctor's job.	Hughes 2002; Lorimer 2012

Table 26 indicates that the most frequently reported themes were 'non-medical sources of information', 'implications of poor communication', and 'how to communicate'.

10.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

10.5 Evidence statements

Clinical

- Moderate quality evidence from 8 qualitative studies (n=1927) using semi-structured interviews, web posts, surveys and focus groups, identified 9 themes relating to patients' concerns about their own information sourcing, what their information requirements are and the consequences of poor communication. The 9 themes were:
  1. Poor explanations of possible adverse events or side effects of medications.
  2. Non-medical sources of information.
  3. Management and communication with regards to ADRs.
  4. Implications of poor communication for patients and carers.
  5. Feelings about the experience of having an ADR.
  6. Information needs.
  7. Communication skills.
  8. Linking signs and symptoms to a possible ADR.
  9. Problems with patient information literature.

  The themes that were identified by 4 out of 8 studies were 'non-medical sources of information', 'implications of poor communication', and 'communication skills'. All other themes were reported in only 1 or 2 studies.

Economic

- No relevant economic evaluations were identified.

10.6 Recommendations and link to evidence

Recommendations	**17. Discuss the person's suspected drug allergy with them (and their family members or carers as appropriate) and provide structured written information (see recommendation 10). Record who provided the information and when.** **18. Provide information in line with the recommendations in Patient experience in adult NHS services (NICE clinical guideline 138).** **19. Ensure that the person (and their family members or carers as appropriate) is aware of the drugs or drug classes that they need to avoid, and advise them to check with a pharmacist before taking any over-the-counter preparations.** **20. Advise people (and their family members or carers as appropriate) to carry information they are given about their drug allergy at all times and to share this whenever they visit a healthcare professional or are prescribed, dispensed or are about to be administered a drug.** **<u>Providing information and support to people who have had specialist drug allergy investigations</u>** **For recommendations on referral to specialist services see Chapter 12.** **21. Allergy specialists should give the following written information to people who have undergone specialist drug allergy investigation:** • **the diagnosis – whether they had an allergic or non-allergic reaction** • **the drug name and a description of their reaction (see recommendation 1)** • **the investigations used to confirm or exclude the diagnosis** • **drugs or drug classes to avoid in future** • **any safe alternative drugs that may be used.** **22. Explain to people in whom allergy to a drug or drug class has been excluded by specialist investigation that they can now take this drug or drug class safely and ensure that their medical records are updated.**
Relative values of different outcomes	The outcomes identified by the GDG as most important for decision-making were examples of information or support that led to an improvement in care and the management of drug allergy. The studies included in the review examined many different types of interventions and describe a variety of resulting outcomes. However some common themes emerged around information needs and methods

	of communication which demonstrated both good and bad practice. The GDG considered both the positive and negative outcomes reported in the studies when drawing up recommendations on what information should be given to support patients and the method of communication.
Trade-off between clinical benefits and harms	The GDG agreed that information about drug allergy given to patients is often ad hoc, and written information is rarely given. Providing information that would result in prescribing errors prevented and inappropriate medication being avoided would enable patients to avoid future drug allergic reactions and reduce the number of visits to their GP and emergency admissions to hospital. Providing information on details of the drug taken and the reaction along with any subsequent specialist investigations undertaken would improve communication between healthcare professionals and both help to prevent people without a drug allergy being incorrectly labelled as having an allergy, and ensure that people with a drug allergy avoid drugs to which they may be allergic. The gathering of this information is necessary in order to complete the patient's medical record (see Documentation, Chapter 9), but once collected it should also be shared with the patient. The importance of communication with patients who have had a suspected or confirmed drug allergy was highlighted by studies which described the fear of having a repeat reaction and the anxiety experienced by parents of children with a suspected drug allergy. The group agreed that a dialogue between the healthcare professional and the patient who has had a suspected or confirmed allergic reaction, or their carer, is important to ensure that opportunities are given to ask questions and to provide reassurance as well as practical advice.
Economic considerations	No relevant economic evidence was identified. The GDG did not prioritise this question for original economic analysis. The GDG expected that the impact on time and resource use of providing information to patients would be very small, and would be likely to be offset by an improvement in quality of life. Specifically, provision of information will help people to avoid the suspected allergen in the future, thereby reducing future costs to the health service and future impacts on quality of life through inadvertent repeat exposure. Good provision of information and discussion with a patient at the first opportunity may also reduce time spent by healthcare professionals in providing additional information and explanation to people on future occasions.
Quality of evidence	All of the included studies were qualitative research studies. The quality of each study was assessed in terms of confidence in the study, measured against 14 quality criteria specific to qualitative studies. Seven of the 8 included studies were given a 'moderate' level of confidence and 1 was given 'low' confidence. The 3 most frequently reported themes were non-medical sources of information, the implications of poor communication and how to communicate. The GDG acknowledged the implications of poor communication with patients, especially the fear felt by patients, and stressed the importance of providing clear and comprehensive information at both non-specialist and specialist visits. The GDG also referred to the recommendations given in NICE clinical guideline138 'Patient experience in adult NHS services'[122] to emphasise good patient experience. Recommendations on checking to ensure that patients have the necessary knowledge, and on giving patients the responsibility to carry and share their drug allergy information are intended to minimise patients' fear, enhance communication between patients, clinicians and pharmacists, and enable the patient to better manage their confirmed or suspected drug allergy.
Other considerations	This review is closely connected with the review on documentation

	strategies (see Chapter 9). The quality of patient information can be improved through better documentation strategies and vice versa. The recommendations given here therefore advocate completion and maintenance of drug allergy documentation by healthcare professionals, provision of information to patients with effective communication and retention of that information by the patients.

11 Non-specialist management

In the non-specialist setting a doctor assessing a patient with a suspected allergy to a drug must decide if the drug is the cause of the new symptoms and whether the drug should be continued, the dose altered, or the drug stopped and the person advised to avoid taking the drug again. The course of action taken will be determined by both the severity and nature of the symptoms. If the symptoms are considered expected from the pharmacological profile of the drug, the dose may be altered, which may lead to the symptoms either ceasing or reducing sufficiently to allow the prescription to continue. In some circumstances, treatment may be managed by prescribing an alternative drug. If the allergic reaction to the drug was severe or the person is likely to need the same or a similar drug in future, then referral for specialist investigation may be appropriate as part of the person's continuing management (see Chapter 12).

An area of management where there is some uncertainty is in the provision of an anti-inflammatory drug for people with a suspected allergy to a non-selective non-steroidal anti-inflammatory drug (NSAID). Current usual practice is for people with a suspected allergy to an NSAID to be prescribed an alternative NSAID which may provoke a similar allergic reaction or to use other analgesic agents such as opioids which do not have anti-inflammatory actions and can cause adverse effects. In some cases the individual may be referred to specialist services, giving rise to additional costs. If selective cyclooxygenase 2 (COX-2) inhibitors were found to be a safe alternative to non-selective NSAIDs they could be prescribed in primary care and may avoid the need to refer some people for specialist evaluation and drug challenge.

Selective COX-2 inhibitors

Commonly encountered side effects of NSAIDs include urticaria, angioedema and bronchospasm which affect susceptible patients, such as those with eosinophilic asthma and a history of nasal polyps. These drugs can be prescribed, and some, including aspirin and ibuprofen are also available over the counter, alone and included in a number of compound formulations for common ailments. NSAIDs are some of the most commonly used drugs on account of their anti-inflammatory, analgesic and antipyretic actions. All NSAIDs act on the prostaglandin pathway by inhibiting the enzyme cyclooxygenase. There are 2 main isoforms of cyclooxygenase – COX-1 and COX-2 – and both are inhibited to varying degrees by the available NSAIDs in a ratio that is unique to each drug. Inhibition of COX-1 is considered responsible for many of the allergic and some of the adverse reactions associated with these drugs.

Since the introduction of selective COX-2 inhibitors a number of studies have sought to examine whether patients reporting allergic reaction to non-selective NSAIDs will nonetheless tolerate selective COX-2 inhibitors. Experience from UK specialist drug allergy centres indicates that the majority of patients with a clinical history of allergy to non-selective NSAIDs tolerate selective COX-2 inhibitors, but each patient has usually received a hospital drug challenge under close monitoring to confirm tolerance.

11.1 Review question: In patients who have had allergic reactions to NSAIDs what are the factors that indicate whether they can or cannot tolerate selective COX-2 inhibitors?

For full details see review protocol in Appendix C.

Table 27: Characteristics of review question

Population	Patients who have had a previous allergic reaction to NSAIDs

Presence of factors or defining characteristics	• History of an allergy to more than 1 type of NSAIDs
	• History of concurrent allergies
	• History of comorbidities
	  ○ Chronic urticaria (with or without angioedema)
	  ○ History of asthma
	  ○ History of nasal polyps
	  ○ History of chronic rhinosinusitis
	• Eosinophilia
	• Age of the patient
	• Severity of the original reaction
	• Concurrent medications

Outcomes	• Incidence and severity of reaction to selective COX-2 inhibitors (coxibs), such as the following:
	  ○ Asthma
	  ○ Angiodema
	  ○ Urticaria
	• Incidence of other adverse events

Study design	Systematic reviews (SRs), prospective cohort studies, case control studies, randomised controlled studies

11.2 Clinical evidence

We searched for any study that reported on tolerance and safety of COX-2 inhibitors in people who have had a previous allergic reaction to an NSAID (including aspirin). Studies that included only COX-2 inhibitors not licenced in the UK (such as nimesulide, rofecoxib, and valdecoxib) were excluded. We also excluded retrospective case reviews. Thirty-five observational studies were identified.[4,7,10,11,25,26,28,35,37,39,53,55,57,72,81,83,98,99,107,114,119,127,128,133,136,138-140,142,148,149,164,168,169,172] All studies were prospective cohort studies using either single or multiple drug COX-2 challenges, and were by study design mainly single blinded. They usually used incremental dosages (with a washout period between different drugs to prevent carry-over effects). There was considerable variation in study populations. Those could be divided into the following categories:

- Studies including only participants with a history of cutaneous reactions to NSAIDs.
- Studies including only participants who had asthma exacerbated by NSAIDs.
- Studies with mixed populations.
- One study restricted to people with anaphylactoid reactions to NSAIDs.

Results are described according to the COX-2 inhibitor used in the challenge test. The following drugs were tested:

Selective COX-2 inhibitors:

- celecoxib
- etoricoxib
- parecoxib (administered intravenously).

Preferential COX-2 inhibitors:

- etodolac
- meloxicam
- nabumetone.

In the vast majority of studies incremental dosages were used for oral challenges. At which dosage the reaction occurred was therefore also noted.

Table 29 summarises the evidence with regards to tolerance to those drugs. See also the study selection flow chart in Appendix E and exclusion list in Appendix K.

Summary of included studies

The characteristics of included studies are briefly outlined in Table 28 – for details please see Appendix H.

Table 28: Summary of studies included in the review

Study	Population	Drug and dose, mg	NSAID sensitivity confirmed	Protocol	Patients reacting n (%)
Andri & Falagiani, 2007[4]	Patients with previous cutaneous reactions to NSAIDs (asthma induced by NSAIDs excluded)	Celecoxib 50 mg or 75 mg or 100 mg	No	Single-blind prospective cohort	3/32 (0.9%)
Asero, 2007[7]	Patients with chronic urticaria with NSAID intolerance	Etoricoxib 30–60 mg	No	Single-blind prospective cohort	0/17 (0%)
Bavbek et al. 2004[10]	Patients with a history of urticaria or angioedema, naso-ocular symptoms, bronchospasm or anaphylactoid reactions to NSAIDs.	Meloxicam 7.5 mg	No	Single-blind prospective cohort	5/61 (8.1%)
Bavbek et al. 2007[11]	Patients with asthma or nasal polyps who are hypersensitive to aspirin	Meloxicam 7.5 mg	Yes	Single-blind prospective cohort	1/21 (4.8%)
Celik et al. 2005[25]	Patients with a history of urticaria or angioedema, naso-ocular symptoms, bronchospasm or anaphylactoid reactions to NSAIDs.	Celecoxib 200 mg in divided doses	No	Single-blind prospective cohort	0/75 (0%)
Colanardi et al. 2008[26]	Patients with previous cutaneous reactions to NSAIDs	Parecoxib 40 mg	No	Single-blind prospective cohort	0/79 (0%)
Confino et al. 2003[28]	Patients with a history of hypersensitivity reaction to at least 2 different NSAIDs (patients suffering from asthma or chronic urticaria were not included)	Nabumetone 1000 mg	No	Prognostic cohort study; open oral challenge	2/24 (8.3%)
Domingo et al. 2006[35]	Patients with a history of any type of allergic reaction, reactions to at least 2 different NSAIDs, or positive oral challenge to aspirin	Meloxicam 7.5 mg	No	Single-blind prospective cohort	5/108 (5%)
Dona et al.	Group A with any type of	Etoricoxib 15 mg,	Yes	Single-blind	Group A:

Study	Population	Drug and dose, mg	NSAID sensitivity confirmed	Protocol	Patients reacting n (%)
2011[37]	intolerance to NSAIDs and paracetamol and Group B with sensitivity to NSAIDs only	15 mg and 30 mg		prospective cohort	12/47 (25.53%) Group B: 3/50 (6%)
El Miedany et al. 2006[39]	Patients with a history of asthma induced by aspirin and at least 1 other NSAID	Etoricoxib 60 mg or 90 mg or 120 mg	No	Single-blind prospective cohort	0/77 (0%)
Garcia-Rodriguez, 2002[53]	Patients with a history of urticaria or angioedema after ingestion of at least 2 different NSAIDs (separate episodes)	Celecoxib 200 mg	No	Single-blind prospective cohort	0/20 (0%)
Goksel et al. 2010[55]	Patients with a history of urticaria or angioedema triggered by 1 or more NSAIDs	Meloxicam 7.5 mg	No	Single-blind prospective cohort	10/116 (8.6%)
Gyllfors et al. 2003[57]	Patients with asthma and aspirin intolerance	Celecoxib, 10 mg or 30 mg or 100 mg or 200 mg	No	Double-blind placebo-controlled crossover oral challenge followed by an open challenge	0/33 (0%)
Inomata et al. 2007[72]	Patients with a history of urticaria or angioedema after NSAID intake	Etodolac 200 mg Meloxicam 10 mg	Yes	Single-blind prospective cohort	Etodolac 8/15 (53.3%) Meloxicam 2/6 (33.3%)
Kleinhans et al. 2002[81]	Patients with a history of any type of allergic reaction NSAID sensitivity	Celecoxib 200 mg	No	Prospective comparative cohort, 2 phase approach: 1) scratch and patch test; 2) single-blind placebo-controlled oral challenge protocol	0/14 (0%)
Koschel et al. 2013[83]	Patients with a history of respiratory disease exacerbated by aspirin	Etoricoxib 10 mg or 30 mg or 60 mg	Yes	Single-blind prospective cohort	3/104 (3%)
Liccardi et al. 2005[99]	History of cutaneous reactions to paracetamol and NSAIDs.	Celecoxib 200 mg	Yes	Single-blind prospective cohort	1/29 (3.4%)
Llanora et al. 2003[100]	Patients with a history of any type of allergic reaction NSAID sensitivity	Etoricoxib Cumulative dose of 120 mg but given in separate	No	Prospective cohort	4/74 (5.4%)

Study	Population	Drug and dose, mg	NSAID sensitivity confirmed	Protocol	Patients reacting n (%)
		doses, 30 minutes apart			
Martin-Garcia et al. 2003[107]	Patients with asthma exacerbated by aspirin	Celecoxib 50 mg or 75 mg or 100 mg	No	Single-blind prospective cohort	0/33 (0%)
Mihaela et al. 2012[114]	Patients with a history of urticaria or angioedema triggered by 1 or more NSAIDs	Etoricoxib 60 mg	No	Single-blind prospective cohort	2/118 (1.69%)
Muratore et al. 2007[119]	Patients with a history of urticaria or angioedema after the ingestion of 2 or more different NSAIDs (on different occasions)	Etoricoxib 100 mg	No	Single-blind prospective cohort	3/37 (8%)
Nettis et al. 2005[128]	Patients with a history of urticaria or angioedema in reaction to NSAIDs	Etoricoxib 100 mg	No	Single-blind prospective cohort	2/141 (1.4%)
Nettis et al. 2001[127]	Patients with a history of cutaneous reactions triggered by 1 or more NSAIDs	Meloxicam 7.5 mg	No	Single-blind prospective cohort	2/148 (1.35%)
Pagani et al. 2010[133]	Patients with a history of any type of allergic reaction NSAID sensitivity	Etoricoxib 90 mg	No	Single-blind prospective cohort	4/139 (2.8%)
Prieto et al. 2007[136]	Patients with either respiratory or cutaneous reactions to NSAIDs	Nabumetone 1–2 g Meloxicam 7.5–15 mg	Yes	Single-blind prospective cohort	9/55 (16.4%) tolerated 2 g dose Nabumetone 2/51 (3.9%) tolerated 15 mg Meloxicam
Quaratino et al. 2000[138]	Patients with a history of any hypersensitivity reactions to 1 or more NSAIDs	Meloxicam 7.5 mg	No	Single-blind prospective cohort	2/177 (1.1%)
Quiralte et al. 2004[139]	Patients with a history of anaphylactoid reactions to NSAIDs	Celecoxib 200 mg	Yes	Single-blind prospective cohort	0/25 (0%)
Roll et al. 2006[140]	Patients with a history of hypersensitivity reactions to 1 or more NSAIDs	Celecoxib 175 mg cumulative dose	Yes	Single-blind prospective cohort	5/106 (4.7%)
Sanchez Borges et al. 2007[142]	Patients with a history of NSAID induced urticaria or angioedema	Meloxicam 15 mg Celecoxib 200 mg Etoricoxib 120 mg	Yes	Single-blind prospective cohort	Meloxicam 6/29 (20.6%) Celecoxib: 14/76 (18.4%) Etoricoxib: 7/62 (11.2%)

Study	Population	Drug and dose, mg	NSAID sensitivity confirmed	Protocol	Patients reacting n (%)
Senna et al. 2003[149]	Patients with a history of at least 1 allergic reaction of any kind to 1 or more NSAIDs	Meloxicam 7.5–15 mg	No	Single-blind prospective cohort	4/381 (1%)
Senna et al. 2004[148]	Patients with a history of at least 1 allergic reaction to 1 or more NSAIDs – divided into 3 groups: NSAID-induced rhinitis and asthma Multiple NSAID-induced urticaria or angioedema Single NSAID-induced urticaria or angioedema	Celecoxib 100–200 mg Meloxicam 7.5–15 mg	No	Single-blind prospective cohort	Celecoxib: 4/72 (6.56%) Meloxicam 3/73 (4.1%)
Valero et al. 2011[164]	Patients with asthma exacerbated by aspirin	Parecoxib 40 mg	No	Single-blind prospective cohort	0/10 (0%)
Viola et al. 2005[168]	Patients with a history of any hypersensitivity reaction to 1 or more NSAIDs	Celecoxib 50–200 mg	No	Single-blind prospective cohort	1/120 (0.8%)
Viola et al. 2007[169]	Patients with a history of any hypersensitivity reaction to 1 or more NSAIDs	Etoricoxib 120 mg	Yes	Single-blind prospective cohort	0/31 (0%)
Woessner et al. 2002[172]	Patients with asthma exacerbated by aspirin	Celecoxib 100–200 mg	Yes	Double-blind prospective cohort	0/60 (0%)

11.2.1 Summary of events induced by COX-2 inhibitors in NSAID-sensitive patients according to the specific drug administered

Table 29: COX-2 reactions, mode and severity and evidence quality

Drug	Number of studies	N	Reactors (mean %; median % across studies)	Type of event							Severity	Quality[a]
				Urticaria	Angioedema	Rhinitis	Airway obstruction	Gastro-intestinal	Pruritus	Erythema		
Celecoxib	13	749	29 (3.8; 0)	16	9		1		2	1	All apart from 1 (a case of moderate angioedema of the lips[b]) described as non-severe	VERY LOW
Etoricoxib	10	823	36 (4.3; 2.3)	10	7		4 (see severity column)		15		Mainly non-severe – 4 cases described as moderate or severe (3 of those asthma attacks and 1 had an asthma attack with tachycardia)	VERY LOW
Parecoxib	2	89	0									VERY LOW
Etodolac	1	15	8 (53.3; n/a)	4	2		2 (see severity column)				Described as non-severe (dyspnea and bronchial asthma and urticaria or	VERY LOW

Drug	Number of studies	N	Reactors (mean %; median % across studies)	Type of event							Severity	Quality[(a)]
				Urticaria	Angioedema	Rhinitis	Airway obstruction	Gastro-intestinal	Pruritus	Erythema		
											angioedema)	
Meloxicam	10	878	42 (4.8; 4.6)	20	10	1	3 (see severity column)	1	2	5	Mainly non-severe (2 asthma attacks and 1 severe bronchial obstruction)	VERY LOW
Nabumetone	2	94	15 (16; 8.3)	7	1		3 (see severity column)		2	2	Mainly moderate to severe (nasal or bronchial symptoms with PEF decreases by more than 15%)	VERY LOW

(a) Evidence quality was assessed according to NICE cohort quality criteria. Weight was given to double-blinding, and also to patient selection (clear description or grouping of patients according to prognostic criteria). Quality was then assessed across studies for each COX-2 drug. All evidence can be considered indirect since prognostic factors were not the objective of the majority of studies.

(b) Described by authors as moderate, symptoms resolved in less than 2 hours after administration of oral cetirizine (10 mg) and intravenous methyl prednisolone (40 mg).

11.2.2 Prognostic factors

History of asthma versus history of cutaneous reactions

Seven studies[11,39,57,83,107,164,172] investigated tolerance to COX-2 inhibitors in people who have asthma that is exacerbated by aspirin and NSAID use. Twelve other studies[4,7,26,37,55,72,114,119,128,142,143,168] addressed tolerance to COX-2 inhibitors restricted to people who have had a previous cutaneous reaction to NSAIDs. In the asthma studies 4 people from an overall 338 (1.1%) had an allergic reaction (0/126 to celecoxib, 3/181 to etoricoxib, 1/21 to meloxicam, and 0/10 to parecoxib) compared to 74 (7.4%) out of 999 in the cutaneous studies (19/282 to celecoxib, 29/472 to etoricoxib, 18/151 to meloxicam, and 0/79 to parecoxib).

History of allergic reaction to single versus multiple drugs

Four studies[36,98,133,148] separated people into groups of people who had a single drug reaction and people with multiple drug reactions or restricted the population to people with multiple drug reactions.

- Liccardi and colleagues (2005)[98] administered an oral challenge with celecoxib to people who had an allergy to NSAIDs as well as to paracetamol. Of the 29 people in this study 1 (3.4%) person experienced a moderate reaction (angioedema of the lips) to the COX-2 inhibitor. Cross-intolerance with paracetamol was also investigated by Dona et al. (2011)[36] in a study with 2 participant groups. In group A, people were intolerant to NSAIDs as well as paracetamol whereas group B was intolerant to NSAIDs only. Reactions to an etoricoxib challenge were more frequent in group A (12/47, 25.5%) compared to group B (3/50, 6%).
- In the study by Pagani et al. (2010)[133] patients were divided into people with previous reactions to a single NSAID (n=83) and people who had previous reactions to multiple NSAIDs (n=56). The tolerability of etoricoxib was evaluated in these groups. The COX-2 inhibitor was not tolerated in 3 of the single reactors (causing wheals in the face area) and in 1 of the multiple reactor group (a severe generalised reaction occurring 3 hours after drug intake).
- Senna and colleagues (2004)[148] divided people into 3 groups of those with a history of NSAID-induced asthma and rhinitis (group A, n=24), a history of multiple drug- (including NSAID-) induced urticaria or angioedema (group B, n=34) and people with NSAID-induced urticaria or angioedema (Group C, n=18). Patients underwent challenge tests with celecoxib and meloxicam. All people in group A tolerated these drugs whereas 3 people in group B, had a skin reaction (2 after celecoxib and 1 after meloxicam) and 4 people in group C (2 to celecoxib and 2 to meloxicam).

Severity of initial reaction to NSAIDs

One study (Quiralte et al. 2004[139]) focused on tolerance to COX-2 inhibitors in people who had had an anaphylactoid reaction (urticaria or angioedema plus hypotension or laryngeal oedema) after NSAID intake on admission to the emergency department. None of the 25 patients who were challenged with celecoxib experienced an allergic reaction.

Mixed population studies

In the remaining studies COX-2 inhibitor challenges were carried out in patients with any previous reactions to NSAIDs. Apart from an overall rate of tolerance, it was unclear which prognostic factors may indicate who may experience COX-2 hypersensitivity in these studies.

11.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

The GDG considered the unit costs of selective COX-2 inhibitors and their alternatives – see Table 39 in Chapter 12 (Referral).

11.4 Evidence statements

Clinical

Tolerance to different types of COX-2 inhibitors in people with a history of hypersensitivity to NSAIDs divided by drug

Selective COX-2 inhibitors:

- Celecoxib – Very low quality evidence from 13 observational studies of people with a history of allergic reactions to NSAIDs (n=749) indicate a low rate of people reacting to celecoxib (mean 4.1%, median 0.4%). The majority of reactions were urticaria and angioedema. One reaction was described as a case of moderate angioedema of the lips, but apart from this all were described as non-severe.
- Etoricoxib – Very low quality evidence from 10 observational studies (n=823) showed a low rate of reactions to etoricoxib (mean 4%, median 2.3%). Drug reactions were mainly described as non-severe. However, there were 4 people who had a moderate to severe reactions, 3 of those had asthma attacks and 1 had an asthma attack with tachycardia.
- Parecoxib – Very low quality evidence from 2 observational studies (n=89) did not report any allergic reactions to parecoxib.

Preferential COX-2 inhibitors:

- Etodolac – Very low quality evidence from 1 observational study (n=15) reported 8 people (>50%) who reacted to etodolac. All reactions were described in the study as non-severe but included dyspnoea, bronchial asthma and urticaria or angioedema.
- Meloxicam – Very low quality evidence from 11 observational studies (n=895) showed that meloxicam had a low rate of allergic reactions (mean 5%, median 4.6%). The majority of reactions were urticaria. However, 1 person` (0.1%) had a severe bronchial obstruction.
- Nabumetone – Very low quality evidence from 2 observational studies (n=94) indicated a comparatively higher rate of drug reaction to nabumetone (16%). Reactions were described as moderate or moderate to severe (mainly respiratory).

Prognostic factors

History of asthma exacerbated by NSAIDs versus history of cutaneous reactions to NSAIDs:

- Very low quality evidence from 7 observational studies with participants with asthma exacerbated by NSAIDs (n=338) and 12 observational studies with participants who had previous cutaneous reactions to NSAIDs (n=1070) indicate that there were fewer overall drug allergic reactions to

COX-2 inhibitors associated with the studies conducted with people with asthma compared to the overall rate of studies restricted to people with a history of cutaneous reactions to NSAIDs.

History of single versus multiple drug allergies:

- Very low quality evidence from 1 study (n=29) reported a rate of 3.4% (1/29) of people who had a history of allergic reactions to NSAIDs and also paracetamol, had a reaction to celecoxib.
- Very low quality evidence from 1 observational study (n=139) showed similar rates of allergic reactions to etoricoxib in people with prior reactions to single NSAID drugs versus people with prior reactions to multiple NSAIDs. However, the 3.6% (3/83) of people in the single NSAID group who reacted, experienced mild reactions whereas the 1.8% (1/56) of people in the multiple NSAID group who reacted, had a severe drug reaction.
- Very low quality evidence from 1 observational study of people with a history of asthma and rhinitis induced by NSAIDs (n=76) using a drug challenge with celecoxib and meloxicam showed a zero rate of reactions. In a group with a history of multiple drug-induced urticaria or angioedema, 6% reacted to celecoxib and 3% to meloxicam; whereas 11% reacted in the group with NSAID-induced urticaria or angioedema (to either celecoxib or meloxicam).

Severity of initial reaction:

- Very low quality evidence from 1 observational study (n=25) showed good tolerance to celecoxib in people with a history of anaphylactic reactions to NSAIDs with none of the study participants reacting to the drug challenge.

Economic

- No relevant economic evaluations were identified.

11.5 Recommendations and link to evidence

Recommendations	**<u>General</u>** **23.If drug allergy is suspected:** • **consider stopping the drug suspected to have caused the allergic reaction and advising the person to avoid that drug in future** • **treat the symptoms of the acute reaction if needed; send people with severe reactions to hospital** • **document details of the suspected drug allergy in the person's medical records (see recommendations 10 and 13)** • **provide the person with information (see Chapter10).** **24.Refer people to a specialist drug allergy service if they have had:** • **a suspected anaphylactic reaction (also see Anaphylaxis, NICE clinical guideline 134) or** • **a severe non-immediate cutaneous reaction (for example, drug reaction with eosinophilia and systemic symptoms [DRESS], Stevens–Johnson Syndrome, toxic epidermal necrolysis).** **<u>Non-steroidal anti-inflammatory drugs (including selective</u>**

	cyclooxygenase 2 inhibitors) **25. Explain to people with a suspected allergy to a non-selective non-steroidal anti-inflammatory drug (NSAID) (and their family members or carers as appropriate) that in future they need to avoid all non-selective NSAIDs, including over-the-counter preparations.** **26. For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:** • **discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy)** • **consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.** **27. Do not offer a selective COX-2 inhibitor to people in a non-specialist setting if they have had a severe reaction, such as anaphylaxis, severe angioedema or an asthmatic reaction, to a non-selective NSAID.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: the incidence and severity of reactions to selective COX-2 inhibitors including asthma, angioedema and urticaria, and the incidence of other adverse events. Although reactions to selective COX-2 inhibitors in the asthmatic group were shown to be less frequent than in the cutaneous group, the GDG agreed that the clinical consequences of an asthmatic reaction were greater than those of a cutaneous reaction.
Trade-off between clinical benefits and harms	On average, across all studies, more than 95% of people with a history of allergy to non-selective NSAIDs were shown to tolerate selective COX-2 inhibitors. Reactions described were generally of mild to moderate severity. The studies demonstrated that celecoxib, etoricoxib and meloxicam were tolerated by people with a history of allergy to NSAIDs (% reactors ≤5%). The GDG noted that meloxicam is a preferential COX-2 inhibitor (only partially selective) and therefore there is a theoretical risk of allergic reaction at higher doses in people with a history of allergic reaction to non-selective NSAIDs. The majority of the studies assessing the use of meloxicam used a single dose challenge with a low dose of 7.5 mg. Two studies considered parecoxib which reported no adverse reactions but these were both very small studies. Parecoxib is only used perioperatively and is usually administered intravenously. The studies frequently reported the level of severity in those who had an adverse reaction, and they were on the whole described as mild to moderate. The severity of an allergic reaction to an NSAID correlates with the dose, and although the risk of a reaction to a selective COX-2 inhibitor appears low, the GDG concluded that people receiving selective COX-2 inhibitors should begin treatment with a single dose taken at the lowest possible starting dose on the first day. It was noted that most studies included in the review all used a sub-therapeutic dose level to start with and increased the dose up to a therapeutic level when the lower dosage was tolerated.

	In studies with people who had asthma exacerbated by NSAIDs there were lower numbers of reactions to selective COX-2 inhibitors than in studies of people who had a history of cutaneous reactions to NSAIDs.
Economic considerations	No relevant economic evidence was identified. The GDG did not prioritise the use of specific COX-2 inhibitors for original economic analysis. The economics of broader aspects of non-specialist management were considered in relation to the reviews of referral to specialist drug allergy services (see Section 12.8). The GDG discussed that if an anti-inflammatory is required, an individual with a suspected allergy to a non-selective NSAID would need either to be referred to specialist drug allergy services or to take a selective COX-2 inhibitor. Provision of selective COX-2 inhibitors is substantially less costly than referral, and given the low risk of a reaction identified by the clinical evidence, the GDG did not feel that referral would offer great clinical benefit. Therefore a strategy of offering a selective COX-2 inhibitor to patients who require an anti-inflammatory but have a suspected non-severe allergy to non-selective NSAIDs would be cost effective, but a strategy of referring all individuals with suspected allergy to non-selective NSAIDs to specialist drug allergy services would not be. (If an anti-inflammatory is not required, then the individual should use an alternative painkiller rather than either a selective or a non-selective NSAID – see Section 12.9 in the review of referral to specialist care.) People who have had a severe reaction to a non-selective NSAID should still be referred to specialist services on grounds of clinical safety.
Quality of evidence	The aim of the included studies was to assess the rate of reactions after a challenge with a non-selective COX-2 inhibitor. The majority of the studies were not designed to address the characteristics that indicate tolerance to selective COX-2 inhibitors. The quality of evidence was rated as very low. However, the quantity of evidence and consistency of results across the included studies increased the GDG's confidence in the findings. None of the studies were randomised and the majority were single-blind, placebo-controlled, single group designs. Many studies did not prove NSAID sensitivity before drug challenges. The evidence demonstrated that there were fewer reactors to selective COX-2 inhibitors in studies restricted to people with prior asthmatic reactions than studies with people with a history of cutaneous reactions to NSAIDs. However, the picture was less clear when comparing people with a history of reactions to those with reactions to multiple NSAIDs.
Other considerations	People who have had a reaction to a drug, for example a cutaneous reaction, would have a similar cutaneous reaction on subsequent exposure. The GDG agreed it is important for people to be advised that they should not take any other type of NSAID (including over-the-counter preparations), other than those they are prescribed. The GDG noted that paracetamol is well tolerated in the majority of people who have had an allergic reaction to non-selective NSAIDs. The GDG acknowledged that this was an important area of management in which to conduct a systematic review. Current practice is for people with a history of allergy to non-selective NSAIDs to be referred for specialist assessment, whereas the review has demonstrated that the majority of this group, other than those who have had severe reactions to NSAIDs, are able to tolerate selective COX-2 inhibitors. The GDG concluded that selective COX-2 inhibitors should be considered for people who have had a previous suspected drug allergic reaction to a non-selective NSAID when there is a need for an anti-inflammatory effect; as a simple analgesic is not adequate to treat symptoms, and when the

	benefits outweigh the low risk of a cutaneous reaction. The benefits and harms should be fully discussed between the GP and the individual when making a joint decision on whether to prescribe. There were lower numbers of reactions to selective COX-2 inhibitors in studies of people who had asthma exacerbated by NSAIDs than in studies of people who had a history of cutaneous reactions to NSAIDs. The GDG agreed people with asthma are a higher risk group and therefore they should not be prescribed any NSAID in primary care, including selective COX-2 inhibitors. The GDG thought that selective COX-2 inhibitors would not be an appropriate treatment for people with rheumatoid arthritis who require long-term treatment that impacts on the severity of the disease and there are treatments specific for rheumatoid arthritis which are preferred. The GDG discussed the need to make general management recommendations for non-specialist settings. Whilst acknowledging that these would state what was already common practice amongst GPs and other healthcare professionals, it was agreed that not providing general principles of management would leave a gap within the guideline.

12 Referral to specialist drug allergy services

Within each drug class a significant proportion of patients develop adverse drug reactions, but the proportion who experience an allergic reaction is considerably lower. For example up to 10% of the population consider themselves to be allergic to penicillin, however it is likely that only a small percentage (perhaps 10%) of those with a label of penicillin allergy are truly allergic, with the remainder having experienced non-allergic side effects or viral exanthems mislabelled as allergy. Referral for specialist investigation should allow either confirmation of the allergy or to have the drug allergy excluded, enabling the patient to have the same and related drugs in future. Even when drug allergy is confirmed, in many cases it will be possible to identify alternative drugs that the patient is able to take safely.

Referral of all patients with a label of drug allergy is not necessarily the appropriate action, as this would be very costly and could overwhelm specialist drug allergy services, while some patients may receive only very small benefits from referral. Therefore, an evidence review has been conducted of the drugs most commonly leading to a referral for further investigation to consider who should be referred to specialist drug allergy services.

12.1 Review question 1: What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to beta-lactam antibiotics?

12.2 Review question 2: What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to NSAIDs?

12.3 Review question 3: What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to local anaesthetics?

12.4 Review question 4: What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected anaphylaxis due to drug allergy during general anaesthesia?

A single search was conducted for the review questions relating to referral of patients with suspected drug allergy.

For full details see review protocol in Appendix C.

Table 30: Main common characteristics of the review question protocol

Population	Patients presenting with suspected drug allergy to beta-lactam antibiotics, NSAIDs or local anaesthetics, or anaphylaxis due to drug allergy to general anaesthesia
Intervention	Referral to specialist drug allergy services (for diagnosis, further investigations to identify safe alternatives or other management strategies)
Comparison	No referral

Outcome	The benefit associated with referral as assessed by: 1. Mortality 2. Number of repeat drug allergic reactions (including patient reported episodes) 3. Length of hospital stay 4. Inappropriate avoidance of drugs. 5. Health-related quality of life Any outcomes that may indicate who should be identified for referral

12.5 Clinical evidence

The aim of the current review was twofold:

1. To assess the benefit of referral plus management by specialist allergy services versus management in primary care.
2. To identify who should be referred to specialist allergy services.

No direct high quality evidence was identified to answer the review questions. Only 1 study (Frigas 2008[51]) was identified which provided indirect evidence for the benefits of referral; see Table 31, GRADE Table 32 and Appendix J for forest plots. The quality of this evidence was assessed as 'Very Low.'

12.5.1 Benefit of referral

Table 31: Benefits of referral to specialist clinics compared to other methods of evaluation for patients with suspected drug allergy to beta-lactam antibiotics

Reference	Population and setting	Aims of study	Effect sizes	Quality of evidence
Frigas et al. 2008[51]	Patients at the Mayo Clinic attending the Preoperation Evaluation Clinic (POEC) with HOAP who were evaluated and skin tested by an allergist and a team of allergy nurses before the decision of which antibiotic to use for POABP was made. Compared to OPES where there was no consultation or testing.	To compare the selection of the antibiotic for POABP in the POEC and OPES setting	Patients with history of beta-lactam allergy: Screened at POEC: 68% cephalosporin, 26% vancomycin, 22% other Screened at OPES: 33% cephalosporin, 26% vancomycin, 41% other. No patients were skin test positive.	Strengths: Study conducted prospectively. There was a baseline difference in age with people screened in non-preoperative evaluation clinics being older than those who received preoperative specialist screening. The analysis was then adjusted for this difference. Quality: Very Low

Abbreviations: HOAP: history of allergy to penicillin; OPES: other preoperative evaluation settings: POABP: perioperative antibacterial prophylaxis; POEC: Preoperation Evaluation Clinic

Table 32: GRADE quality assessment: referral to specialist drug allergy services

Quality assessment							Summary of Findings Effect				Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screened at 'Preoperative Evaluation Clinic (POEC)' setting Event rate (%)	Screened at 'Other non-POEC (OPES)' settings Event rate (%)	Effect size: Relative Risk (95% CI)	Effect size: Absolute effect (95% CI)		
Referral for suspected penicillin allergy (Frigas 2008[51])												
Use of cephalosporin for preoperative prophylaxis in patients with history of beta-lactam allergy (6-month follow-up; assessed with: Mayo Clinic records)												
1	observational study	very serious[a]	no serious inconsistency	very serious indirectness[b]	no serious imprecision	none	280/412 (68%)	23/69 (33.3%)	RR 2.04 (1.45 to 2.87)	347 more per 1000 (from 150 more to 623 more)	⊕OOO VERY LOW	IMPORTANT
Use of vancomycin for preoperative prophylaxis in patients with history of beta-lactam allergy (6-month follow-up; assessed with: Mayo Clinic records)												
1	observational study	very serious[a]	no serious inconsistency	very serious indirectness[b]	no serious imprecision[c]	none	42/412 (10.2%)	18/69 (26.1%)	RR 0.39 (0.24 to 0.64)	159 fewer per 1000 (from 94 fewer to 198 fewer)	⊕OOO VERY LOW	IMPORTANT
Use of cephalosporin for preoperative prophylaxis in patients with penicillin allergy (6-month follow-up; assessed with: Mayo Clinic records)												
1	observational study	very serious[a]	no serious inconsistency	very serious indirectness[b]	serious imprecision	none	254/365 (69.6%)	18/46 (39.1%)	RR 1.78 (1.23 to 2.57)	305 more per 1000 (from 90 more to 614 more)	⊕OOO VERY LOW	IMPORTANT
Use of vancomycin for preoperative prophylaxis in patients with penicillin allergy (6-month follow-up; assessed with: Mayo Clinic records)												
1	observational study	very serious[a]	no serious inconsistency	very serious indirectness[b]	no serious imprecision	none	36/365 (9.9%)	13/46 (28.3%)	RR 0.35 (0.20 to 0.61)	184 fewer per 1000 (from 110 fewer to 226 fewer)	⊕OOO VERY LOW	IMPORTANT

(a) This is an observational study with limited baseline data and only 2 possible confounders are adjusted in the analysis.

(b) The study does not directly address the benefits of referral as such, but seems to indicate that specialist clinics are better than non-specialist services at identifying who has an allergy.

(c) The confidence interval crossed the default MID of 1.25 RR (from benefit to no effect) and was therefore downgraded once.

12.6 Economic evidence

12.6.1 People with suspected allergy to beta-lactam antibiotics

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

12.6.1.1 Cost-effectiveness analysis

In the absence of cost-effectiveness evidence, unit costs were collected to inform qualitative discussions of the cost effectiveness of referral compared to non-specialist management (see Table 33 and Table 34). Hypothetical scenarios were also constructed to further facilitate the GDG's consideration of cost effectiveness in common scenarios (see Table 35–Table 38).

Costs of non-specialist management

In order to calculate the cost of non-specialist management (that is, avoiding drugs to which there is a possible allergy and treating with alternative drugs instead), the GDG considered the costs of the alternative drugs which would be prescribed instead of beta-lactam antibiotics for a person with a suspected allergy to a beta-lactam (see Table 33).

Table 33: Unit costs of beta-lactam and alternative antibiotics

Antibiotic	Group or class	Dosage (adult unless stated)[a]	Duration	Cost per course
Beta-lactams				
Penicillin V	Penicillin	500 mg every 6 hours	7 days	£2.80
Amoxicillin	Penicillin	500 mg every 8 hours	7 days	£1.61
Flucloxacillin	Penicillin	500 mg every 6 hours	7 days	£2.49
Cefalexin	First generation cephalosporin	500 mg every 8 hours	7 days	£1.90
Cefaclor	Second generation cephalosporin	250 mg every 8 hours	7 days	£6.80
Cefixime	Third generation cephalosporin	400 mg once daily	7 days	£26.46
Piperacillin with tazobactam	Penicillin	4000 mg piperacillin with 500 mg tazabactam every 8 hours	14 days	£352.80
Aztreonam	Monobactam	2000 mg every 8 hours	14 days	£790.44
Alternatives to beta-lactams				
Azithromycin	Macrolide	500 mg once daily	3 days	£4.51
Clarithromycin	Macrolide	250 mg every 12 hours	7 days	£1.89
Erythromycin	Macrolide	500 mg every 6 hours	7 days	£3.38
Erythromycin ethyl succinate	Macrolide	40 mg/kg daily (divided into 3 doses)[b]	3 days[b]	£2.57
Doxycycline	Tetracycline	200 mg once on first day; then 100 mg once daily	1 day; 6 days	£1.11
Oxytetracycline	Tetracycline	500 mg every 6 hours	7 days	£2.46
Metronidazole	Nitroimidazole	400 mg every 8 hours	7 days	£1.46

Source: Dosages and prices from British National Formulary (BNF), March 2014[74]

(a) Where BNF gives a range of appropriate dosages, the highest dosage applicable for standard conditions has been chosen, but not any increased doses which may be used, for example, in the case of severe infections. Where durations are not stated in BNF they are as advised by GDG members.
(b) GDG assumption for children with otitis media. Calculations assume a child of 30 kg.

To allow accurate comparison with the costs of referral, these costs must be calculated over a person's lifetime. The cost of non-specialist management ($Cost_{2nd\ line}$) is therefore calculated using the following formula:

$$Cost_{2nd\ line} = cost\ of\ second\ line\ antibiotic\ \times lifetime\ episodes$$

This formula requires an estimate of the number of times an individual will require a beta-lactam over the course of their life (lifetime episodes), which is hugely variable. Therefore, for each scenario, the costs were calculated using 3 different estimates of the number of lifetime episodes (see Table 35–Table 37).

Note that the cost of non-specialist management calculated here is likely to be an underestimate of the true full cost, as it does not take into account higher rates of antibiotic resistance with some second-line treatments, or additional costs incurred due to second-line treatments being less effective at treating the initial infection. The GDG agreed that in some cases this would lead to requirement for a longer course of treatment or the additional use of a third-line antibiotic. The GDG also noted that beta-lactams are generally well tolerated, whereas some second- or third-line antibiotics may cause adverse effects resulting in prolongation of treatment and ill health.

Costs of referral to specialist drug allergy services

Table 34 shows the costs of referral appointments with a drug allergy specialist, which include various components. Generally, if more than 1 test is conducted, the cost to the NHS of that appointment is the cost associated with the most expensive test conducted during that appointment. Therefore, if all 3 tests are conducted, the cost is £499.89, whereas if only the skin prick test is conducted, the cost is £486.08. Table 34 shows that appointments that include intradermal testing are the most expensive and will be undertaken in 95% of cases, and appointments that include a skin prick test will be the most expensive in the remaining 5% of cases. Therefore, we can calculate the total expected cost of a referral appointment ($Cost_{appointment}$) using the following formula:

$$Cost_{appointment} = 0.95 \times £499.89 + 0.05 \times £486.08 = £499.20$$

Table 34: Costs of referral appointments with a drug allergy specialist

Component	Unit cost	Probability test conducted[(d)]
Skin prick test	£486.08[(a)]	100%
Intradermal test	£499.89[(b)]	95%
Drug challenge	£380.22[(c)]	95%

(a) NHS reference costs[33] for day case procedures JC11Z
(b) NHS reference costs[33] for day case procedures JC18Z
(c) NHS reference costs[33] for day case procedures WA20Y
(d) Based on GDG assumptions

However, the cost of the referral appointment is not the full cost of referral as the person will still receive antibiotics when needed in future – whether they can now safely take some or all beta-lactams again or need to use alternatives. People who are found to be truly allergic will still require alternative drugs, and will therefore still incur the additional cost and quality of life impact associated with second-line treatments. The GDG noted that the proportion of people with suspected allergy who are found to be truly allergic is low, estimated to be around 10%. The remaining people are able

to resume taking first-line beta-lactam treatments. Assuming this is correct, the true cost of referral ($Cost_{referral}$) can be estimated as:

$$Cost_{referral} = Cost_{appointment} + 0.9 \times (cost\ of\ first\ line\ antibiotic \times lifetime\ episodes) + 0.1 \times Cost_{2nd\ line}$$

For each scenario the cost of referral ($Cost_{referral}$) is calculated, and compared to the cost of non-specialist management ($Cost_{2nd\ line}$). The gain per episode in quality of life required for referral to be cost effective at the £20,000 per QALY gained threshold is then calculated based on the following formula:

$$QALY\ gain\ required\ per\ episode = incremental\ cost\ of\ referral \div £20{,}000 \div lifetime\ episodes$$

This gives the number of additional QALYs that someone who has had a referral appointment (and hence now has a 90% chance of being able to take a first-line beta-lactam antibiotic, and a 10% chance of taking a second-line alternative antibiotic during future episodes requiring antibiotics) would gain during each future episode requiring an antibiotic compared to the quality of life of someone under non-specialist management who would take a second-line antibiotic during the same episode. This figure is also presented in terms of quality-adjusted life days (QALDs).

Scenario 1

An adult presents with an acute throat infection. The first-line treatment is assumed to be penicillin V, and the second-line treatment is assumed to be erythromycin. Results of the analysis are reported in Table 35.

Table 35: Scenario 1: acute throat infection

Lifetime episodes	Cost of non-specialist management	Cost of referral to a drug allergy specialist	Incremental cost of referral	QALYs (QALDs) required per episode for referral to be cost effective at a threshold of £20,000 per QALY gained
2	£6.76	£504.91	£498.15	0.0125 (4.5)
5	£16.90	£513.49	£486.59	0.0050 (1.8)
10	£33.80	£527.78	£483.98	0.0025 (0.9)

Scenario 2

A child presents with otitis media. The first-line treatment is assumed to be amoxicillin, and the second-line treatment is assumed to be erythromycin ethyl succinate. Results of the analysis are reported in Table 36.

Table 36: Scenario 2: otitis media in children

Lifetime episodes	Cost of non-specialist management	Cost of referral to a drug allergy specialist	Incremental cost of referral	QALYs (QALDs) required per episode for referral to be cost effective at a threshold of £20,000 per QALY gained
2	£5.14	£502.61	£497.47	0.0124 (4.5)
5	£12.85	£507.73	£494.88	0.0049 (1.8)
10	£25.70	£516.26	£490.56	0.0025 (0.9)

Scenario 3

An adult presents with bronchiectasis and associated respiratory exacerbation. The first-line treatment is assumed to be amoxicillin (although note this is assumed to be taken for 14 days rather than the standard 7-day course), and the second-line treatment is assumed to be clarithromycin. Results of the analysis are reported in Table 37. Scenario 3 differs from the preceding scenarios as bronchiectasis can lead to recurrent respiratory exacerbation, which sometimes requires specialist treatment, and on occasion may lead to hospital admission and the need for intravenous antibiotics. The doses required are higher than the standard dose (clarithromycin 500 mg twice daily) and each treatment course would last for 14 days not 7 days. An individual who has bronchiectasis may require antibiotics multiple times in a year, leading to a significant impact on quality of life, and increased costs, if amoxicillin cannot be used due to a suspected drug allergy. Also note that the additional cost per course of antibiotics is higher in this scenario than in the preceding scenarios.

Table 37: Scenario 3: bronchiectasis leading to recurrent respiratory sepsis

Lifetime episodes	Cost of non-specialist management	Cost of referral to a drug allergy specialist	Incremental cost of referral	QALYs (QALDs) required per episode for referral to be cost effective at a threshold of £20,000 per QALY gained
5	£37.80	£517.47	£479.67	0.0048 (1.8)
10	£75.60	£535.74	£460.14	0.0023 (0.8)
20	£151.20	£572.28	£421.08	0.0011 (0.4)

Scenario 4

An adult with cystic fibrosis presents with a respiratory infection. The first-line treatment is assumed to be piperacillin with tazobactam, and the second-line treatment is assumed to be aztreonam. Note that these are both beta-lactam antibiotics, however there is thought to be little cross-reactivity between these drugs. Regardless of the class of antibiotic, referral is still required to investigate whether the first-line treatment needs to be avoided. Results of the analysis are reported in Table 38. In this scenario, the referral strategy is cheaper than providing the expensive second-line treatment. Referral is also expected to increase quality of life compared to no referral, therefore referral is expected to dominate no referral in this scenario. The QALYs required for referral to be cost effective at the threshold of £20,000 per QALY gained would therefore be negative, and so are not calculated.

Table 38: Scenario 4: cystic fibrosis

Lifetime episodes	Cost of non-specialist management	Cost of referral to a drug allergy specialist	Incremental cost of referral	QALYs (QALDs) required per episode for referral to be cost effective at a threshold of £20,000 per QALY gained
5	£3,952.20	£2,482.02	−£1,470.18	Not applicable – referral dominates
10	£7,904.40	£4,464.84	−£3,439.56	Not applicable – referral dominates
20	£15,808.80	£8,430.48	−£7,378.32	Not applicable – referral dominates

Other considerations

Note that this cost comparison does not calculate the QALY gains associated with either referral or non-specialist management. The GDG stressed that second-line treatments are not only more costly than most first-line treatments, but are generally less effective at treating infections and have worse side effect profiles. In cases where second-line treatments are not tolerated well this may lead to third-line treatment, which is likely to be even less effective at treating the initial infection. Second- and third-line treatments are likely to lead to longer recovery times and reduced quality of life during recovery compared to first-line antibiotics. Consequently referral is likely to lead to improvement in

quality of life compared to non-specialist management, as 90% of individuals will be able to resume taking first-line treatments.

Where second-line treatments are not tolerated well this may also lead to additional GP appointments, and additional interventions may also be required to counter side effects associated with second- and third-line treatments, the costs of which have not been included here. Consequently, the true cost of non-specialist management is likely to be higher than calculated here, and the incremental cost of referral lower.

The GDG also noted that this analysis does not account for the possibility that bacteria may be resistant to second-line antibiotics. This is more common with second-line treatments than with first-line treatments, and again may necessitate the use of less effective third-line treatments.

12.6.2 People with suspected allergy to NSAIDs

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

In the absence of cost-effectiveness evidence, unit costs were collected to inform qualitative discussions of the cost effectiveness of referral compared to non-specialist management.

Costs of non-specialist management

In order to consider the cost of non-specialist management (that is, avoiding drugs to which there is a possible allergy and treating with alternative drugs instead), the GDG noted the costs of the alternative drugs which would be prescribed instead of NSAIDs for a person with a suspected allergy to NSAIDs (see Table 39).

Table 39: Costs of selected NSAIDs and alternatives

Drug	Maximum daily dose (adult)	Maximum daily cost
NSAIDs – non-selective		
Aspirin	4000 mg	£0.52
Ibuprofen	2400 mg	£0.23
Naproxen	1000 mg	£0.12
NSAIDs – selective COX-2 inhibitors		
Celecoxib (Celebrex)	400 mg	£1.44
Etoricoxib (Arcoxia)	90 mg	£0.82
Parecoxib (Dynastat)	80 mg (intramuscular or intravenous injections)	£9.92
NSAIDs – preferential COX-2 inhibitors		
Etodolac	600 mg	£0.27
Meloxicam	15 mg	£0.04
Nabumetone	2000 mg	£0.56
Alternative painkillers		
Paracetamol	4000 mg	£0.22
Co-dydramol	80 mg dihydrocodeine	£0.26

Drug	Maximum daily dose (adult)	Maximum daily cost
	4000 mg paracetamol	
Co-codamol (8/500)	64 mg codeine 4000 mg paracetamol	£0.13
Co-codamol (30/500)	240 mg codeine 4000 mg paracetamol	£0.37
Codeine	240 mg	£0.40
Dihydrocodeine	120 mg	£0.17
Tramadol	400 mg	£0.28

Source: Doses and prices from British National Formulary, March 2014[74]

To allow accurate comparison with the costs of referral, these costs would need to be calculated over a person's lifetime. As the frequency of use of NSAIDs varies widely depending on the condition and individual the GDG did not think it was appropriate to create scenarios for NSAIDs, but considered the costs of NSAIDs and alternative drugs along with the likely frequency of their use when formulating the recommendations relating to NSAIDs.

Alternative painkillers listed in this table do not have direct anti-inflammatory effects, and so will not be appropriate alternatives for all conditions for which an NSAID may be used, and will have different side effect profiles to NSAIDs.

Costs of referral to specialist drug allergy services

Table 40 shows the costs of referral appointments with a drug allergy specialist that include various components. Generally, if more than 1 test is conducted, the cost to the NHS of that appointment is the cost associated with the most expensive test conducted during that appointment. Therefore, if all 3 tests are conducted, the cost is £499.89, whereas if only the skin prick test is conducted, the cost is £486.08. Table 40 shows that appointments that include intradermal testing are the most expensive and will be undertaken in 95% of cases, and appointments that include a skin prick test will be the most expensive in the remaining 5% of cases. Therefore, we can calculate the total expected cost of a referral appointment ($Cost_{appointment}$) using the following formula:

$$Cost_{appointment} = 0.95 \times £499.89 + 0.05 \times £486.08 = £499.20$$

Table 40: Costs of referral appointments with a drug allergy specialist

Component	Unit cost	Probability test conducted[(d)]
Skin prick test	£486.08[(a)]	100%
Intradermal test	£499.89[(b)]	95%
Drug challenge	£380.22[(c)]	95%

(a) NHS reference costs[33] *for day case procedures JC11Z*
(b) NHS reference costs[33] *for day case procedures JC18Z*
(c) NHS reference costs[33] *for day case procedures WA20Y*
(d) Based on GDG assumptions

Note that the cost of the referral appointment is not the full cost of referral. People who are found to be truly allergic will still require treatment with alternative drugs, and will therefore still incur the additional costs and quality of life impact associated with second-line treatments. The GDG noted that the proportion of people with suspected allergy who are found to be truly allergic is low, estimated to be around 10%. The remaining 90% of people are able to resume taking NSAIDs.

12.6.3 People with suspected allergy to local anaesthetics

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

12.6.4 People with suspected anaphylaxis due to drug allergy during general anaesthesia

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

12.7 Evidence statements

Clinical

- Very low quality evidence from 1 observational study (n=485) showed a significant increase in the use of cephalosporin and a decrease in the use of vancomycin in a model of practice that used an allergy consultation and skin testing in the selection of the antibiotic compared with a model that did not. Negative skin tests did not preclude the use of alternative drugs.

Economic

- No relevant economic evaluations were identified.

12.8 Recommendations and link to evidence: beta-lactam antibiotics

What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to beta-lactam antibiotics?

Recommendations	**28. Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service 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).** **29. Consider referring people to a specialist drug allergy service if they are not able to take beta-lactam antibiotics and at least 1 other class of antibiotic because of suspected allergy to these antibiotics.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: mortality, repeat drug allergic reactions, length of hospital stay, inappropriate avoidance of drugs, and health-related quality of life. However, these outcomes were not provided in the study reviewed.

	Indirect evidence for these outcomes came from included rates of referral, rates of positive testing and plausibility of adverse drug reactions.
Trade-off between clinical benefits and harms	The evidence presented to the GDG did not provide a sufficient number of outcomes to form the basis for a discussion on the trade-off between clinical benefits and harms. The benefits and harms were therefore discussed based on the experience of the GDG members. The systematic review focussed on beta-lactams, NSAIDs and local and general anaesthetics. However the GDG considered that if a person had experienced anaphylactic or severe cutaneous reactions such as DRESS or Stevens–Johnson Syndrome after taking any drug the person should be referred to specialist services for further investigation. In addition to the serious harm that may be caused to the person, the nature of such a severe reaction would be extremely alarming for the person concerned (and their parent or carer, where relevant), and it would be important to conduct further investigations in order to prevent a repeat occurrence. The GDG agreed that the guideline should provide a clear general recommendation that if these reactions are observed the person needs to be referred. The GDG agreed that for some conditions penicillin is the most effective and safest antibiotic and is associated with fewer side effects than alternative drugs. The GDG noted that in pregnancy penicillin has a good safety profile and some other classes of antibiotics would be contraindicated. The GDG agreed the risk of sensitising people to beta-lactams through carrying out investigations was extremely low. The GDG considered whether there were particular considerations for the referral of children with regards to benefits and safety outcomes. The consensus was that these recommendations apply to all age groups.
Economic considerations	No relevant economic evidence was identified. The GDG identified referral to specialist drug allergy services or alternative management strategies within primary care for patients who are not referred as the highest priority area for original economic analysis. The GDG believed that economic modelling in this area would be informative if feasible, but concluded that modelling was unfortunately not feasible as information was not available on the relative effectiveness of referral or non-specialist management on outcomes such as the number of future allergic reactions or the number of occasions alternative drugs are used. This was due both to the fact that as specialist management is outside the scope of this guideline the referral pathway is undefined, and to the lack of applicable published economic research on the areas that are within the scope. Therefore any model would necessarily have to be built largely upon estimates and assumptions. In particular, sufficient data were not available to allow modelling of different subgroups, which would be necessary to identify which individuals should or should not be referred to specialist drug allergy services. Instead of conducting a full economic evaluation, 4 cost-effectiveness scenarios were constructed for the case of suspected allergy to beta-lactam antibiotics. These calculated the potential costs of both referral to specialist drug allergy services and of non-specialist management for multiple frequencies of future need for antibiotics. They presented the magnitude of difference in quality of life which referral would need to be expected to yield for it to be cost effective compared to non-specialist management. The GDG used these scenarios to inform their recommendations regarding which people should and should not be

referred to specialist drug allergy services, as discussed below.

People who have experienced a suspected anaphylactic reaction or a severe non-immediate cutaneous reaction

The GDG considered this to be an issue of patient safety: severe reactions need to be investigated and referral is necessary for appropriate future treatment to be identified. Appropriate investigation of an allergy after anaphylaxis or a severe non-immediate cutaneous reaction will allow safe treatments to be identified and given in future, and will therefore avoid the large cost and quality of life impacts of further reactions. The GDG agreed that these recommendations would be appropriate across drug allergy generally, and should not be restricted only to people who have had such severe reactions to beta-lactams. The GDG noted that this represents a small patient group, and is therefore not expected to have a large impact on resources.

People who need treatment for a disease which can only be treated by a beta-lactam

The GDG considered that referral was the only appropriate option for this group of patients as it is crucial to determine which drugs they can take safely. This is an issue of patient safety.

People with a high likelihood of future need for beta-lactams

The GDG discussed the economic implications of referral and non-referral. It was noted that if patients are not referred they typically remain under an assumed positive diagnosis and will in future be given second-line antibiotics which are often more expensive and less effective than first-line beta-lactams. Referral, on the other hand, leads to the cost of a specialist appointment and allergy investigations. If upon referral a patient is found not to have a drug allergy, they can return to taking the first-line treatment, and thus some savings and improvements in quality of life would be realised.

The GDG considered several hypothetical scenarios in which patients present with a range of infections for which beta-lactams are typically considered first-line treatments. The GDG considered the cost of a referral strategy compared to a non-specialist management strategy for each scenario, as well as the QALYs required for the referral strategy to be cost effective at a cost-effectiveness threshold of £20,000 per QALY gained. The GDG also discussed the limitations of this approach, notably that the analysis did not account for the higher rates of antibiotic resistance associated with some second-line treatments, nor did it quantitatively measure the decrease in quality of life associated with taking second-line treatments. The analysis was therefore considered to underestimate the benefits of referral.

The analysis confirmed that second-line treatments are often more expensive than first-line beta-lactams, and showed that a key driver of cost effectiveness was the number of times in an individual's life they would require beta-lactams. For example, a patient who has an acute throat infection and would only require beta-lactam treatment twice more over their lifetime would need to gain 0.0124 QALYs (or 4.52 quality-adjusted life days) from referral during each future treatment episode compared to treatment with second-line drugs, which was not considered likely. However, a patient with bronchiectasis who requires beta-lactams 20 times over their lifetime would only need to gain 0.0011 QALYs (or 0.41 quality adjusted life days) per treatment episode as a result of being referred for referral to be considered cost effective compared to treatment with second-line drugs. The GDG agreed that the QALY gain in the latter case would be likely to be reached. Therefore the GDG concluded that referral is likely to be cost effective for patients who

	have a high likelihood of frequent need for beta-lactams. **People with suspected allergy to beta-lactams and another class of antibiotics** It is important to establish which antibiotics are safe for people in this population group to take. This can only be done reliably and safely through referral, therefore the GDG considered that referral was the only appropriate strategy for this group of patients, and is necessary to ensure patient safety. The GDG also noted that whilst there is a cost of referral, this will be partially offset by a reduction in the number of patients taking third-line treatments, which can be considerably more expensive, and could be counteracted by an increase in quality of life.
Quality of evidence	Overall the evidence is sparse and of very low quality and only provides indirect evidence to the question of benefits of referral and characteristics of people who might benefit from referral.
Other considerations	The aim of the review was to assess the benefit of referral and to determine who should be referred to specialist drug allergy services. As only indirect evidence was found the recommendations are based on the cost-effectiveness scenarios and the consensus view of the GDG. The GDG did not consider that patients who have a history of allergy should be automatically investigated unless a beta-lactam was the drug of choice and no suitable alternative was available. There is a case for investigating particular groups such as people with immune deficiencies or recurrent infections who have a greater need for antibiotic drugs. Similarly people with a history of adverse reactions or allergy to more than one class of antibiotic have a restricted choice of antibiotic and therefore specialist referral for this group was considered necessary as otherwise alternative antibiotics may be less effective, more expensive or have greater side effects. The GDG agreed that patients who are allergic to 2 or more classes of antibiotics also have increased anxiety and this may impact on their quality of life. The GDG also observed that alternative antibiotics are sometimes more complicated to administer and monitor and may sometimes require prolonged hospital admission for intravenous administration. The GDG noted that, in UK practice, it would not be usual to give cephalosporins (which have low levels of cross-reactivity with other beta-lactams) to people allergic to beta-lactams for pre-surgical prophylaxis; however they are used fairly widely on hospital wards.

12.9 Recommendations and link to evidence: NSAIDs

What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to NSAIDs?

Recommendations	**30. Refer people who need treatment with an NSAID to a specialist drug allergy service if they have had a suspected allergic reaction to an NSAID with symptoms such as anaphylaxis, severe angioedema or an asthmatic reaction.** **31. Be aware that people with asthma who also have nasal polyps are likely to have NSAID-sensitive asthma unless they are known to have tolerated NSAIDs in the last 12 months.**
Relative values of different	The following outcomes were identified by the GDG as important for

outcomes	decision-making: mortality, repeat drug allergic reactions, length of hospital stay, inappropriate avoidance of drugs, and health-related quality of life. No clinical studies were identified for this question.
Trade-off between clinical benefits and harms	The GDG discussed the following benefits and harms associated with referral for NSAID allergies. This discussion was based on the experience of guideline members as no direct evidence was identified. Although many people can avoid NSAIDs or take an alternative analgesic drug such as paracetamol or an opiate, some people require an NSAID for their anti-inflammatory properties. Someone who is allergic to one NSAID should be assumed to be allergic to all other non-selective NSAIDs as well, so should not take any without undergoing specialist investigations to assess which NSAIDs can be safely taken. Those people who have experienced only a mild reaction to a non-selective NSAID should be recommended to take a selective COX-2 inhibitor (see Chapter 11). For those who have experienced a severe reaction and for whom an NSAID would be the preferred treatment option referral is required to determine which NSAID(s) may be safely taken. The GDG noted that patients are also extremely anxious after experiencing a severe reaction and confirmation of whether they can use an NSAID again, now or in the future, can have benefits for the person's quality of life.
Economic considerations	No relevant economic evidence was identified. **People who have had a suspected allergic reaction with severe symptoms and require treatment with NSAIDs** No cost-effectiveness evidence was identified. The GDG discussed the economic implications of referral compared to a non-specialist management strategy; it was noted that if patients are not referred they typically remain under an assumed positive diagnosis and are given alternative treatments. The GDG therefore considered the unit costs of NSAIDs and their alternatives. The cost differences between these are small, with alternatives being cheaper in some cases, and referral comes at a much higher cost. The GDG considered that in some cases the alternative treatments are not as effective, and therefore referral may lead to gains in quality of life (many patients are found not to be allergic following specialist investigation and can resume taking any NSAID). It was also noted that the cost of referral to a drug allergy specialist would only be incurred once, yet the benefits of a confirmed diagnosis would be felt on multiple occasions during a lifetime. The GDG agreed that when NSAIDs are required and selective COX-2 inhibitors cannot be taken the quality of life gained from through referral by identifying NSAID(s) which are safe to take are likely to be substantial, and referral is likely to be cost effective. The GDG noted that this represents only a small group of patients, as alternatives painkillers or selective COX-2 inhibitors can be given in the majority of cases, meaning that non-selective NSAIDs are usually not required. The GDG judged that it would not be cost effective to refer people who do not require treatment with NSAIDs. **People with asthma and nasal polyps** It is believed that people with asthma who also have nasal polyps are likely to be intolerant of NSAIDs. The GDG agreed that, as with the general population, referral would only be cost effective for this group if NSAIDs were required for treatment. In the majority of cases an alternative painkiller could be given instead.
Quality of evidence	No relevant studies were identified for this clinical question.

Other considerations	The recommendations are based on the consensus of the GDG. The GDG were aware of asthma patients being admitted to hospital because they had taken an NSAID and agreed that it is important to ensure this group of patients receive appropriate information to prevent repeated reactions potentially leading to readmission and patient death. The GDG estimated that 5–10% of people with asthma are affected, but agreed further investigation through a drug challenge was not always necessary. People with asthma who have had a reaction to an NSAID should have this flagged within their notes and the patient informed that they should avoid the use of all NSAIDs in future. The GDG were aware that advice provided to all patients with asthma is generally to avoid using an NSAID. However, the group agreed that the presence of particular comorbidities can identify those asthma patients at a higher level of risk such as the presence of chronic rhinosinusitis, a history of nasal polyps, or eosinophilia. The GDG believed that these patients should be provided with written advice on avoidance of NSAIDs but that they should be referred to specialist drug allergy services only if NSAIDs were required for future management of an existing condition.

12.10 Recommendations and link to evidence: local anaesthetics

What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to local anaesthetics?

Recommendations	**32. Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: mortality, repeat drug allergic reactions, length of hospital stay, inappropriate avoidance of drugs, and health-related quality of life. No evidence was found for these outcomes in this review.
Trade-off between clinical benefits and harms	In the absence of direct evidence for this review questions recommendations were based on GDG consensus. A patient who has experienced a suspected drug allergic reaction following the previous use of a local anaesthetic would in some cases be able to receive an alternative local anaesthetic from a different class. However, the healthcare professional (doctor, dentist or anaesthetist) concerned may not recommend an alternative local anaesthetic, depending on which alternative drugs would be appropriate for the required usage and the severity of the previous reaction. In addition some people may be unwilling to receive an alternative local anaesthetic due to their previous experience, even if informed that the likelihood of a reaction with a different class of drug is low. In the case of most procedures using local anaesthetics, the alternative to using a different local anaesthetic is to carry out the procedure under general anaesthesia, although it is noted that in the case of some dental procedures some individuals may choose to undergo the procedure without any anaesthetic. Procedures carried out under general anaesthesia are likely to have similar clinical outcomes, but longer recovery times and an increased rate of adverse events. Dental procedures carried out without anaesthetic will result in increased pain for the individual.

Economic considerations	No relevant economic evidence was identified. The GDG considered the cost of referral to a specialist and weighed this against the alternative strategy of no referral, in which the patient remains under an assumed positive diagnosis. The GDG judged that if a patient was unable to undergo a procedure with local anaesthetic due to a suspected allergy they may suffer substantial decreases in quality of life, or be referred for the procedure under general anaesthetic at a much greater cost. The GDG therefore agreed that in such cases it would be very likely to be cost effective to refer patients to a specialist drug allergy service, as this would allow identification of local anaesthetics which would be safe for the individual to use, thereby avoiding the substantial impact on quality of life of non-treatment or the increased costs of general anaesthetic. The GDG highlighted that patients may need local anaesthetics multiple times over their lifetime, and whilst the cost of referral to a drug allergy specialist would only be incurred once, the benefits of a confirmed diagnosis could be realised on multiple occasions. For those people who are able and willing to receive an alternative local anaesthetic there is no need for referral to a specialist service, and so referral would not be a cost effective strategy.
Quality of evidence	No relevant studies were identified for this clinical question.
Other considerations	GPs do not have the tools to enable them to determine if a patient has an allergy to one or more local anaesthetics. The only way of determining this is to refer to specialist drug allergy services for investigation. In the majority of suspected cases of allergy the patient is found not to be allergic when investigations have been completed and will therefore be able to take the same local anaesthetic. In most other cases the investigation will conclude that the patient may safely take an alternative local anaesthetic. Referral to specialist care therefore enables patients to receive treatment with local anaesthetic as planned, without the need for general anaesthesia. The GDG agreed it is inappropriate to advise a general anaesthetic on the basis of a previous suspected allergic reaction to a local anaesthetic that has not been investigated.

12.11 Recommendations and link to evidence: general anaesthesia

What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected anaphylaxis due to drug allergy during general anaesthesia?

Recommendations	**33. Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia.**
Relative values of different outcomes	The following outcomes were identified by the GDG as important for decision-making: mortality, repeat drug allergic reactions, length of hospital stay, inappropriate avoidance of drugs, and health-related quality of life. No evidence was found for these outcomes in this review.
Trade-off between clinical benefits and harms	In the absence of evidence the GDG discussed risks and benefits based on their experience. If a patient has experienced a suspected allergic reaction or anaphylaxis to a drug during or immediately following general anaesthesia, then it is not safe for the patient to undergo further general anaesthesia until the patient has undergone investigation to determine the cause of the reaction and an

	alternative combination of drugs is identified that may be safely administered to the patient. Referral to specialist care therefore gives benefit in enabling treatment for the original condition to be completed, enabling the patient to undergo procedures under general anaesthesia in future, and in reducing anxiety or stress induced in the patient by uncertainty regarding their condition and concern that they would be unable to undergo emergency procedures in future. These are substantial benefits and most likely outweigh the potential risk of having an allergic reaction to the tests used in specialist investigations.
Economic considerations	No relevant economic evidence was identified. The GDG stressed that this is an issue of patient safety. It is crucial to establish whether or not an individual is allergic to general anaesthesia as there is often no alternative, and this can only be accurately determined through referral to specialist drug allergy services. The GDG also noted that suspected allergy to general anaesthesia can lead to cancelled or postponed surgery or to prolonged hospital stays, either of which would have a large impact on both hospital costs and quality of life. Some people may require general anaesthesia more than once over their lifetime; the cost of referral to a drug allergy specialist would only be incurred once, whilst the benefits of a confirmed diagnosis could be realised on multiple occasions. The GDG therefore considered that referral is very likely to be cost effective for people with a suspected allergy to general anaesthesia.
Quality of evidence	No relevant clinical studies were identified for this review question.
Other considerations	A large proportion of people will require general anaesthesia at some point in their lives, often in an emergency situation, and in most cases such procedures have no alternative to general anaesthesia. A large number of drugs and other agents are administered during a general anaesthetic and therefore the cause of any allergic reaction is often not evident. These may include neuromuscular blocking agents, anaesthetics, antibiotics, NSAIDs, latex and chlorhexidine Consequently, if the cause of a suspected allergic reaction or anaphylaxis is not investigated then the patient is at risk of being unable to receive necessary emergency treatment at some future point in their life. In addition, in many cases where a patient experiences anaphylaxis or a suspected allergic reaction during general anaesthesia the procedure will immediately be terminated, and a further procedure under general anaesthesia may hence be required to complete the original treatment. GPs do not have diagnostic tools to enable them to determine if a patient has an allergy to a drug used in general anaesthesia, or to which of the drugs involved the patient is allergic. The only way of determining this is to refer the patient for investigation by drug allergy specialists. The investigation will normally conclude that the patient may undergo general anaesthetic using an alternative combination of drugs which have been found to be safe for that person. There is limited availability of specialists who can comprehensively investigate allergic drug reactions during general anaesthesia and the GDG noted the particular requirement for highly specialised investigation. The GDG noted that lesser reactions should also be referred, not just life-threatening reactions, and recognised that in current practice a referral may sometimes not be made due to a problem not being identified or lack of knowledge regarding where referrals should be directed. The GDG recognised that it is likely that there is currently under-referral of people with reactions during anaesthesia.

13 Acronyms and glossaries of terms used in the guideline

13.1 Acronyms and abbreviations

Acronym or abbreviation	Description
ADE	Adverse drug event
ADR	Adverse drug reaction
AMP	Ampicillin
AX	Amoxicillin
AXO	Amoxicilloyl c6
BP	Benzyl penicillin
BPO	Benzylpenicilloyl c1
CDS	Clinical decision support
CDR	Challenge–dechallenge–rechallenge
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
CPOE	Computerised physician (or prescriber) order entry
DST	Decision support tool
ED	Emergency department
EID	Extent of information desired
FEIA	Fluoroenzymoimmunoassay
FN	False negative
FP	False positive
HOAP	History of allergy to penicillin
ICD	International Classification of Diseases
IgE	Immunoglobulin E
MDM	Minor determinant mixture
MPE	Medication prescribing error
NMBA	Neuromuscular blocking agent
NPV	Negative predictive value
NRLS	The National Reporting and Learning System
NSAIDs	Non-steroidal anti-inflammatory drugs
OPES	Other preoperative evaluation settings
POABP	Perioperative antibacterial prophylaxis
POEC	Preoperative Evaluation Clinic
PPV	Positive predictive value
QALY	Quality-adjusted life year
QALD	Quality-adjusted life day
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies checklist
RAST	A radioallergosorbent test
RIA	Radioimmunoassay
SD	Standard deviation
SPL	Structured product labelling

Acronym or abbreviation	Description
TEN	Toxic epidermal necrolysis
TN	True positive
TP	True negative

13.2 Glossary of medical terms

Term	Definition
Allergological	Relating to the study of allergies.
Anaphylaxis	A serious allergic reaction that is rapid in onset and may cause death. It typically causes a number of symptoms including an itchy rash, throat swelling, and low blood pressure. Common causes include insect bites and stings, foods, and medications.
Angioedema	The rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues.
Bronchospasm	A sudden constriction of the muscles in the walls of the bronchioles. It is caused by the release (degranulation) of substances from mast cells or basophils under the influence of anaphylatoxins. It causes difficulty in breathing which can be mild to severe.
Cutaneous	Relating to, or affecting the skin.
Dechallenge	A medical testing protocol in which an administered medicine or drug is withdrawn while the patient is being monitored for adverse effects at each stage.
Eosinophilic asthma	A type of asthma that is characterised by increased levels of eosinophils (a type of white blood cell) in the airways.
Exanthemic	A disease or condition, accompanied by a skin eruption.
Extrapyramidal effects or symptoms	Extrapyramidal symptoms (EPS) are various movement disorders such as acute dystonic reactions, pseudoparkinsonism, or akathisia suffered as a result of taking dopamine antagonists, usually antipsychotic (neuroleptic) drugs, which are often used to control psychosis. They can also be symptoms of metabolic diseases.
Hypotension	Low blood pressure, especially in the arteries of the systemic circulation.
IgE	Immunoglobulin E (IgE) is 1 of the 5 subclasses of antibody related to allergic reactions present in the blood, usually in very low concentrations or found on the surface of cells such as mast cells.
IgE testing	A test that measures the blood level of IgE. The IgE test is often performed as part of an initial screen for allergies.
IgE-mediated	When triggered by an allergen (usually proteins in certain food) the body releases antibodies to fight what it thinks are offending cells. This leads to an increase in histamine levels in the body and the classic allergic reactions (such as inflammation of the face and limbs and anaphylaxis). This reaction can be measured by blood tests as there will be an increase of IgE levels in the blood; these are known as IgE-mediated allergies.
Maculopapular rash	A type of rash characterised by a flat, red area on the skin that is covered with small confluent bumps.
Nasal polyps	Abnormal tissue growths that grow inside the nasal passages and sinuses.
Naso-ocular	Of or pertaining to the nose and eyes.
Non-IgE-mediated	In non-IgE allergic reactions the person suffers with some of the same

Term	Definition
	symptoms, but does not make IgE antibodies against the allergens.
Peri-anaesthetic anaphylaxis	Anaphylaxis during surgical and interventional procedures involving anaesthetic.
Pharmacia Uni CAP FEIA system	New solid-phase immunoassay, fully automated, used for the volumetric analysis of specific IgE antibodies.
Pharmacovigilance	Also known as Drug Safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.
Prostaglandin pathway	The route of alteration and chemical breakdown of prostaglandins in the human body.
Radioallergosorbent test (REIA)	A blood test used to determine to what substances a person is allergic.
Rechallenge	A medical testing protocol in which an administered medicine or drug is re-administered while the patient is being monitored for adverse effects at each stage.
Rhinosinusitis	Inflammation of the para-nasal sinuses. It can be due to infection, allergy, or autoimmune problems.
Serum tryptase	Tryptase is a trypsin-like proteinase that is most abundant in human mast cells and basophils.
Skin prick tests	A skin prick test introduces a tiny amount of allergen into the skin, eliciting a small, localised allergic response, in the form of a wheal (bump) and flare (redness) at the site of testing.
Stevens–Johnson syndrome	A life-threatening skin condition, in which cell death causes the epidermis to separate from the dermis. The syndrome is thought to be a hypersensitivity complex that affects the skin and the mucous membranes. The most well-known causes are certain medications, but it can also be due to infections, or more rarely, cancers.
Tachypnoea	Also known as or related to hyperpnoea, rapid respiration, rapid shallow breathing, breathing fast, tachypneic, respiratory rate raised.
Tryptase	The most abundant secretory granule-derived serine proteinase contained in mast cells and has been used as a marker for mast cell activation.
UniCAP	A highly sensitive laboratory method for detection of serum tryptase using fluorescence linked to an antibody
Urticaria	Urticaria (also known as hives, welts or nettle rash) is a raised, itchy rash that appears on the skin. The rash can be limited to 1 part of the body or spread across large areas of the body.
Viral exanthems	A widespread rash usually occurring in children. Exanthems can be caused by toxins or drugs, microorganisms, or can result from autoimmune disease.

13.3 Glossary of methodological terms

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the

Term	Definition
	individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive a particular intervention, for example placebo arm
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers or doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are

Term	Definition
	sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional that provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences.

Term	Definition
	Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.

Term	Definition
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or

Term	Definition
	because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 × QALYs gained) minus Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Loss to follow up	Participants in a study who were lost to follow up.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of

Term	Definition
	the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant.

Term	Definition
	For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can

Term	Definition
	be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.

Term	Definition
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6-months pregnant, a very sensitive test would detect everyone who was 6-months pregnant, but would probably also include those who are 5- and 7-months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5-months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6-months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be:

Term	Definition
	• manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

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