National Clinical Guideline Centre

Draft for Consultation

Drug allergy

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

Clinical guideline <...>

Appendices A–M

April 2014

Draft for Consultation

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Appendices

Appendix A: Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

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

1.1 Short title

Drug allergy

2 The remit

The Department of Health has asked NICE: 'To produce a clinical guideline on Drug allergy: diagnosis and management of drug allergy in adults and children

3 Clinical need for the guideline

3.1 Epidemiology

a) The World Health Organisation (WHO) uses the following definition of a "drug": "A term of varied usage. In medicine, it refers to any substance with the potential to prevent or cure disease or enhance physical or mental welfare, and in pharmacology to any chemical agent that alters the biochemical physiological processes of tissues or organisms". The European Commission further define a medicinal product as, "any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis."

b) An adverse drug reaction is defined by the European commission as "a response to a medicinal product which is noxious and unintended". ADRs can be classified into reactions, which may affect anyone (type A) and reactions which, affect only susceptible individuals (type B). Within the definition of drug allergy we have also included any reaction presenting with symptoms commonly associated with immune-mediated reactions such as urticarial, angioedema or asthma because the mechanism at presentation may not be evident from clinical history. True hypersensitivity reactions are immune-mediated and classified into Gell and Coombs categories. Drug allergy requires prior exposure to the same or a cross-reacting compound (sensitization) at a dose tolerated by the majority of individuals. Therefore there may not be a history of prior exposure to the specific drug. A variety of mechanisms underpin the allergic symptoms, experienced with subsequent courses of drug.

c) Diagnosing a drug allergy is challenging, with considerable variation in service provision, practice and referral pattern. This can lead to under-diagnosis, misdiagnosis and self-diagnosis.

d) There is no robust information on the prevalence or incidence of drug allergy alone in the UK population. Information is available for adverse drug reactions of which drug allergy is a subgroup, and anaphylaxis for which drug allergy is a potential cause.

e) The estimated incidence of drug allergy in primary care shows that the incidence in women is twice as high as that in men. The reason for this is unclear.

Adverse drug reactions

f) Analysis of observational data has estimated that 6.5% of all hospital admissions in England occur because of adverse drug reactions. The Hospital Episode Statistics database for England,

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from 1996–2000 reports a lower figure of 0.083%. It is unclear what proportion is because of drug allergy.

Anaphylaxis

g) Available estimates suggest that approximately 1 in 1333 people in England have experienced anaphylaxis at some point in their lives. This figure represents all cases and all causes of anaphylaxis. The proportion of cases of anaphylaxis because of drug allergy or other causes (such as allergic reaction to food or an insect bite) was not estimated.

Mortality and morbidity

h) The BSACI guideline on drug allergy reported a UK study which estimated that 0.32% of serious adverse drug reactions were fatal. The guidance does not estimate what proportion of these hospital admissions, prolonged stays, or deaths were attributable to drug allergy.

Risk factors

i) The BSACI guideline reports that the most important risk factor for drug allergy is a history of previous reaction to the same or related compound.

3.2 Current practice

a) There is variation in referral patterns and in the management of drug allergies. There is also variation in geographical access to specialist allergy centres, as most of the centres are located in cities. The variation may relate to a lack of knowledge of available services or a lack of local provision of a drug allergy centre. Therefore, only a proportion of people are likely to be treated in specialist allergy centres whereas others are never referred and remain in primary care. Some people have their drug allergy managed within other disciplines. For example, cancer centres may manage drug allergies related to their own treatment regimes.

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b) The drugs commonly investigated/referred include: penicillins, other beta-lactam antibiotics, non-beta-lactam antibiotics, drugs given during general anaesthesia (for example neuromuscular blocking agents), local anaesthetics, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors, radio-contrast media and plasma expanders.

c) The investigation of a drug allergy includes:

- assessing previous history of drug reactions and allergies
- taking a blood tryptase test at the time of the allergic reaction and when the patient has recovered
- performing a skin prick test, an intradermal test, a patch test and specific IgE testing (only available for a limited number of drugs)
- conducting a drug provocation test (controlled administration of a drug to diagnose drug hypersensitivity reactions).

d) Tests undertaken during an acute reaction to confirm or exclude diagnosis may include:

- Serum tryptase, urea and electrolytes, liver function test, full blood count, differentiated blood count, Coombs' test, antinuclear antibody, antineutrophil cytoplasmic, antibody erythrocyte sedimentation rate, blood coagulation tests and C-reactive protein.
- skin biopsy
- urine microscopy
- electrocardiogram
- chest X-ray.

e) Managing an adverse drug reaction with a possible immunological cause (including drug allergy) involves identifying alternative drugs, drug avoidance, advice and drug desensitisation.

f) People are often labelled as having drug allergy which can lead to lifelong avoidance of certain drugs, particularly antibiotics.

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However, studies that performed skin prick test, intradermal test or oral challenge on people who have had a plausible history of drug allergy showed that most were able to tolerate the drug.

g) People who have experienced an adverse event during anaesthesia are often anxious about the possibility of needing surgery in the future and, unless the cause is investigated and diagnosed, they may actively avoid referral for future surgical treatment, with a consequent risk to their health.

This NICE guideline is needed to address the known and unknown variations in the diagnosis and management of drug allergies.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (19 years and older), young people and children with suspected and confirmed drug allergy (0 – 18 years old).

b) No patient subgroups have been identified as needing specific consideration.

4.1.2 Groups that will not be covered

a) None.

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4.2 *Healthcare setting*

a) All settings where care is commissioned or provided by the NHS.

4.3 *Clinical management*

4.3.1 Key clinical issues that will be covered

a) Information and support needs of patients, carers and parents when appropriate, in all settings

b) Signs and symptoms of a drug allergy to identify possible drug allergy.

c) Documenting drug allergy, which may include the documentation and communication of suspected and confirmed drug allergies across all NHS primary and secondary care, dental services and by all healthcare professionals including drug allergy specialists

d) Use of diagnostic tests including, serum tryptase and serum specific immunoglobulin E (IgE).

e) Management by non-drug allergy specialists including avoidance, safe alternatives and referral.

f) Referral to a drug allergy specialist. Particular consideration will be given to the referral of people with suspected drug allergies to the following: local anaesthetics,, beta lactams, NSAIDs in people with asthma and allergic reactions during general anaesthesia.

4.3.2 Clinical issues that will not be covered

a) Other allergies (for example food allergies).

b) Treatment of the acute phase including anaphylaxis.

c) Investigation of allergies to individual drugs and populations (unless specified in included section).

d) Treatment of non-allergic adverse drug reactions.

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4.4 *Main outcomes*

a) Mortality.

b) Medication errors

c) Length of hospital stay.

d) Acute admission and/or readmission into secondary care.

e) Number of contacts with healthcare professionals (for example with GP).

f) Inappropriate avoidance of drugs.

g) Health-related quality of life.

4.5 *Economic aspects*

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions or strategies. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 *Status*

4.6.1 Scope

This is the consultation draft of the scope. The consultation dates are 3–31 October 2012.

4.6.2 Timing

The development of the guideline recommendations will begin in December 2012.

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5 Related NICE guidance

- Anaphylaxis. NICE clinical guideline 134 (2011).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).

6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

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Appendix B: Declarations of interest

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B.1 Introduction

All members of the GDG and all members of the NCGC staff were required to make formal declarations of interest at the outset of each meeting, and these were updated at every subsequent meeting throughout the development process.

No interests were declared that required actions.

B.2 GDG members

B.2.1 Arden-Jones, Mike

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

B.2.2 Cousins, David

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	Apologies	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

B.2.3 Doyle, Matthew

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	
GDG Meeting 1	14/12/2012	N/A	
GDG Meeting 2	25/01/2013	N/A	
GDG Meeting 3	02/05/2013	No change	

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	**Personal pecuniary interest**: Paid for writing an article on Allergic Rhinitis for the Guidelines in Practice magazine.	No action required.
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	Apologies	
GDG Meeting 11	06/06/2014		

1 **B.2.4 Du Toit, George**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	No action required.
GDG Meeting 1	14/12/2012	Apologies	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2013	Apologies	
GDG Meeting 5	19/07/2013	**Non-personal pecuniary interest**: Principal investigator for two food allergy studies. Thermofisher providesthe testing kits.The company also produce ImmunoCap tests for drug allergy.	No action required. Review on serum specific IgE testing presented in GDG3
GDG Meeting 6	16/09/2013	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	Apologies	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

2 **B.2.5 East, Mandy**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Non-Personal pecuniary interest**: Paid as a self-employed contractor for work on the National Allergy Strategy Group who are supported by unrestricted grants from: ALK Abello, Meda Pharma, Damone and Thermo Fisher.	No action required.
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

1 **B.2.6 Ewan, Pamela**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

2 **B.2.7 Larcombe, James**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Personal non-pecuniary interest**: Member of the formulary committee: British National Formulary for Children.	No action required.
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	Apologies	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	Apologies	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

3 **B.2.8 Mundy, Nicola**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Non-personal pecuniary interest**: The national Allergy Strategy Group for whom I am contracted to work on a consultancy basis is funded by industry donations.	No action required.
GDG Meeting 1	14/12/2012	No change	

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

1 **B.2.9 Nasser, Shuaib**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Non-personal pecuniary**: Clinical trial on asthma funded by GlaxoSmithKline Completed March 2012. Current Clinical trial on biological treatment for asthma funded by Aerovance. **Personal non-pecuniary interest**: Chair of the guideline committee of the BSACI Drug allergy advisor to British National Formulary	No action required.
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	**Personal non-pecuniary:** Attendance at a scientific board meeting at GlaxoSmithKline for work related to the development of a vaccine for asthma.	No action required.
GDG Meeting 10	31/01/2014	**Non-personal pecuniary:** Principle Investigator for Asthma trial in receipt of funding from Astra Zeneca.	No action required.
GDG Meeting 11	06/06/2014		

2 **B.2.10 Oborne, Alice**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		Personal non-pecuniary interest: I have written the Allergy Policy and Allergy Procedure for an acute NHS Trust, these documents cover assessment and documentation of patients' reported	No action required.

GDG meeting	Date	Declaration of Interest	Action Taken
		allergies. non-personal pecuniary interest Research grant from FSTT Charity (a healthcare grant-giving body in South London) to assess the impact of a patient-held penicillin allergy card and information booklet, on patient knowledge and empowerment. This work is on-going.	
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	Apologies	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

1 **B.2.11 Whitaker, Paul**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		None	
GDG Meeting 1	14/12/2012	No change	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	No change	
GDG Meeting 5	19/07/2014	Apologies	
GDG Meeting 6	16/09/2014	No change	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	Apologies	
GDG Meeting 11	06/06/2014		

2 **B.2.12 Williams, Andrew**

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		Personal non-pecuniary interest: Council member of the British Society of Allergy and Clinical Immunology. I have held this role from July 2012 to present .	No apologies required.
GDG Meeting 1	14/12/2012	Apologies	
GDG Meeting 2	25/01/2013	No change	
GDG Meeting 3	02/05/2013	No change	

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 4	07/06/2014	Apologies	
GDG Meeting 5	19/07/2014	No change	
GDG Meeting 6	16/09/2014	Apologies	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	Apologies	
GDG Meeting 9	10/01/2014	No change	
GDG Meeting 10	31/01/2014	No change	
GDG Meeting 11	06/06/2014		

B.3 Co-optees

B.3.1 Brown, Nick

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Personal pecuniary interest**: I work as a performer in a NHS dental practice. I am a practice owner of a fully private dental practice.	No action required.
GDG Meeting 1	14/12/2012	N/A	
GDG Meeting 2	25/01/2013	N/A	
GDG Meeting 3	02/05/2013	N/A	
GDG Meeting 4	07/06/2014	N/A	
GDG Meeting 5	19/07/2014	N/A	
GDG Meeting 6	16/09/2014	N/A	
GDG Meeting 7	04/11/2013	No change	
GDG Meeting 8	05/11/2013	No change	
GDG Meeting 9	10/01/2014	N/A	
GDG Meeting 10	31/01/2014	N/A	
GDG Meeting 11	06/06/2014		

B.3.2 Harper, Nigel J N

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Peronal pecuniary interest**: Shares held in GlaxoSmithKline Limited.	No action required.
GDG Meeting 1	14/12/2012	N/A	
GDG Meeting 2	25/01/2013	N/A	
GDG Meeting 3	02/05/2013	N/A	
GDG Meeting 4	07/06/2014	**Personal pecuniary interest**: Completed a project related to a muscle relaxant drug for which he had received a research grant.	No action required.
GDG Meeting 5	19/07/2014	N/A	
GDG Meeting 6	16/09/2014	N/A	
GDG Meeting 7	04/11/2013	N/A	
GDG Meeting 8	05/11/2013	Apologies	
GDG Meeting 9	10/01/2014	N/A	

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 10	31/01/2014	N/A	
GDG Meeting 11	06/06/2014		

B.3.3 Krishna, Thirumala

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Application		**Personal non-pecuniary**: conducting a multi-centre survey on investigations for general anaesthetic allergy. Co-author of British Society for Allergy and Clinical Immunology (BSACI) guideline on 'penicillin allergy' I am a member of BSACI Standards of Care Committee and audit lead.	No action required.
GDG Meeting 1	14/12/2012	N/A	
GDG Meeting 2	25/01/2013	N/A	
GDG Meeting 3	02/05/2013	No change	
GDG Meeting 4	07/06/2014	N/A	
GDG Meeting 5	19/07/2014	N/A	
GDG Meeting 6	16/09/2014	N/A	
GDG Meeting 7	04/11/2013	N/A	
GDG Meeting 8	05/11/2013	N/A	
GDG Meeting 9	10/01/2014	N/A	
GDG Meeting 10	31/01/2014	N/A	
GDG Meeting 11	06/06/2014		

B.4 All NCGC Staff

GDG meeting	Date	Declaration of Interest	Action Taken
GDG Meeting 1	14/12/2012	None	
GDG Meeting 2	25/01/2013	None	
GDG Meeting 3	02/05/2013	None	
GDG Meeting 4	07/06/2014	None	
GDG Meeting 5	19/07/2014	None	
GDG Meeting 6	16/09/2014	None	
GDG Meeting 7	04/11/2013	None	
GDG Meeting 8	05/11/2013	None	
GDG Meeting 9	10/01/2014	None	
GDG Meeting 10	31/01/2014	None	
GDG Meeting 11	06/06/2014		

Appendix C: Clinical review protocols

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C.1 Assessment

Component	Description
Review question	What is the clinical and cost effectiveness of clinical probability scores or algorithms in identifying or excluding drug allergies?
Objective	To investigate whether there are established clinical algorithms or clinical prediction rules that help to identify signs, symptoms, aspects of medical history or risk factors relating to a drug allergy reaction
Population	Patients presenting with signs or symptoms of suspected drug allergy Patients with a record of suspected drug allergy
Interventions	Clinical algorithms or prediction rules that assess likelihood or class patients into likelihood of having a drug allergy or adverse drug reaction
Comparisons	Other algorithms No algorithms, including direct referrals, no referrals
Outcomes	For RCT or comparative cohort studies: • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Acute admission or readmission into secondary care. • Number of contacts with healthcare professionals (for example with GP) • Inappropriate avoidance of drugs • Health-related quality of life • Other health services research-based outcomes, potentially including documentation, adherence to the protocol or some other measures indicating a decrease in error (these may be described narratively) After considering the evidence available, the review focused outcomes on commonalities for assessment of causality shared among algorithms
Study design	• Systematic reviews, RCTs • In the absence of RCTs, cohorts studies may be considered, particularly any multivariate studies used to derive the algorithms
Exclusions	Non-English studies Abstracts
How the information will be searched	Databases: Medline, Embase, CINHL Language: restrict to English only
The review strategy	The most appropriate design is an RCT, or a cluster randomised controlled trial. In the absence of systematic reviews and RCTs, the following study designs will be included: • Prospective and retrospective comparative cohort studies • Diagnostic studies (cross-sectional, cohorts) Apart from analysing the data quantitatively (using meta-analysis where possible), qualitative observations from the studies included will also be summarised narratively. These areas will be included in the narrative description where available: • Key components of the algorithm – what signs, symptoms, aspects of medical history are documented • How was the algorithm derived? For example, expert opinion, multivariate analysis?

	• How was the algorithm implemented? (Was any education or training given? Who conducted it?) • What was the overall conclusion about the algorithm's impact on patient outcomes and clinicians using it? • What elements in the algorithm were helpful? • Did the study authors make suggestions?

C.2 Measuring serum tryptase after suspected anaphylaxis

Component	Description
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?
Objective	To establish whether serum tryptase (mast cell tryptase) testing is useful in the diagnosis of an anaphylactic reaction due to suspected drug allergy
Population	Patients presenting with suspected anaphylaxis. 'Anaphylaxis' is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by rapidly developing life-threatening problems involving any of the following: the airway (pharyngeal or laryngeal oedema) breathing (bronchospasm with tachypnoea) circulation (hypotension or tachycardia) possible associated skin and mucosal changes.
Index test	Conducting a serum tryptase test during an acute reaction
Reference test	Other methods of confirming diagnosis of drug allergy such as skin tests, oral challenge tests or clinical signs and symptoms.
Outcomes	For diagnostic studies: • 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) For RCTs or comparative cohort studies • Mortality • Number of repeat drug allergic reactions (including patient reported episodes) • Inappropriate avoidance of drugs • Length of hospital stay • Acute admission or readmission into secondary care • Number of contacts with healthcare professionals (for example with GP) • Health-related quality of life
Study design	• Diagnostic cohort studies • Systematic reviews, RCTs or comparative cohort studies (which compare the outcomes of a group with test done against a group without any tests done) • If no diagnostic cohort studies, RCTs or comparative studies are found, case–control studies may be considered.
Exclusions	Non-English studies
How the	Databases: Medline, Embase, CINHL

Component	Description
information will be searched	Language: restrict to English only

The review strategy	Data analysis strategy:
	• Results will be subgrouped based on
	  ○ time of test in relation of time of reaction (up to 2 hours, 2–4 hours, more than 4 hours)
	  ○ children versus adults
	  ○ tests done in different settings.
	• There will be no separate analysis or subgrouping based on drug type or manufacturer.

C.3 Measuring serum specific IgE

Component	Description
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?
Objective	To establish whether serum specfic IgE testing is useful in diagnosing or ruling out drug allergies
Population	Patients presenting with signs or symptoms of suspected drug allergy Patients with a record of suspected drug allergy
Index test	Serum IgE test for the following agents: • Amoxicillin • Ampicillin • Cefaclor • Chlorhexidine • Morphine • Penicillin G • Penicillin V • Suxamethonium
Reference test	• Skin tests, oral challenge test or in the case of anaphylaxis, clinical signs and symptoms • No serum specific IgE test (follow-up)
Outcomes	For diagnostic studies: • 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) For RCTs or comparative cohort studies • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Acute admission or readmission into secondary care

Component	Description
	• Number of contacts with healthcare professionals (for example with GP) • Inappropriate avoidance of drugs • Health-related quality of life
Study design	• Diagnostic cohort studies • If no evidence is found in diagnostic studies, RCTs or comparative cohort studies, evidence from case–control studies may be considered.
Exclusions	Non-English studies However, if English language studies are not available for a specific drug, studies in other languages will be considered
How the information will be searched	Databases: Medline, Embase, CINHL
The review strategy	Data analysis strategy: Results for different tests of different drugs will not be pooled (strata-level[(a)] comparison). The following factors may affect the results of the tests and therefore a subgroup[(b)] analysis will be applied: • Tests by different manufacturers or brand names due to variation in technology used • Tests done at different times, for example, within months versus after a few years, serum IgE level may drop after a few years (may vary depending on type of drug or reaction) • Tests done in different settings, for example, in primary care setting for any patient versus in allergy specialist settings with more selective testing criteria (for example, selecting patients with more severe reactions) or better identification of drug allergy patients • Different patient groups: for example, adults versus children

(a) 'Strata': this means we will not combine or pool data in a meta-analysis across different groups. The underlying assumption is that these interventions are different.

(b) When we subgroup data, we think that there the factors which may contribute to some differences observed, but it is uncertain and we will test this where possible. We might still be able to extrapolate data from one group to another.

C.4 Documenting and sharing information with other healthcare professionals

Component	Description
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?
Objective	To investigate the clinical and cost effectiveness of documentation strategies to prevent patients from receiving drugs to which they are allergic
Population	People with suspected or confirmed drug allergies and healthcare professionals in primary or secondary care.
Interventions	• Interventions include both active interventions (for example, alerting systems in e-prescribing) and passive interventions (for example, posters). This list may not be exhaustive. Other interventions identified in the search will also be included. • Patient-held records (including notes, cards, mobile devices) • Information worn by patients: for example MedicAlert bracelets, 'tags' or pendants on patients. These are worn by the patient at all times.

Component	Description

	• Hospital-issued special coloured armbands, wristbands, ankle bands. These are given out by the hospital when a patient comes into hospital.
	• Education materials to raise awareness (for example, posters or leaflets).
	• Automated messages as reminders, for example, screensaver messages.
	• Mandatory reporting of drug allergy status in paper or electronic medication records or in prescription forms or systems. This includes any records (hospital records, GP records) and all prescription forms or systems.
	• Mandatory documentation of details related to the adverse drug reaction, including:
	  ○ Drug name
	  ○ Symptoms
	  ○ Timing or reaction
	  ○ Number of doses taken
	• Mandatory documentation of details of any investigations for suspected drug allergy with any patient records or medical notes.
	• Position of the information or alerts relating to drug allergy status in medical or electronic records (for example, on front of cover, within notes where clinician is most likely to be reading, or on every page or screen).
	• Design of drug charts.
	• Use of Summary of Care Records or similar systems from other healthcare services around the world (that is, standard medical records available to clinicians at all levels of care)
	• Use of electronic systems such as e-prescribing systems, dispensing systems, drug administration systems as methods of improving communication of drug allergy status. Also known as CPOE (computerised physician or prescriber order entry systems).
	• Electronic checks based on barcoding (to prevent giving wrong information by accident).
	• Audit-based initiatives, for example, patient safety.

Comparisons	No intervention or any of the above interventions alone or in combination.
Outcomes	Primary 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 Surrogate outcomes (only extracted if above not reported in sufficient studies): • Mortality • Length of hospital stay • Admission • Other healthcare professional contact (for example with GP)
Study design	• Systematic reviews • RCTs • Observational studies • Before and after studies • Case series • Surveys • Qualitative studies
Exclusions	Non-English studies

Component	Description
How the information will be searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only
The review strategy	Information to be extracted in evidence tables on whether studies report if both absence and presence of drug allergy was documented. If a lot of evidence is identified for a particular intervention then only the higher-level evidence may be included in the review.

C.5 Providing information and support to patients

Component	Description
Review questions	1. What information and support should individuals with suspected drug allergy or their parents and carers receive? 2. What information and support should individuals who have had specialist investigations or their parents and carers receive?
Objective	To investigate the clinical and cost effectiveness of information and support provision for individuals with a suspected drug allergy or their parents and carers
Setting	Information from both primary and secondary care settings will be relevant. Priority will be given to UK and more recent studies in the order of review
Population	Patients (or their family and carers) with history or experience of suspected or diagnosed drug allergy. Studies from the general (healthy) populations such as public surveys about drug allergy will also be included.
Intervention	Information about diagnosis and management of drug allergy
Comparison	None
Evaluation	Patient experiences; preferences; perceptions, including factors which improve or act as barrier of optimal care. Clinical and quality of life outcomes related to diagnosis and management of drug allergy.
Study design	• Qualitative studies (interviews, focus groups, observations) and surveys about perception, experiences and preferences of hand hygiene practice. • Systematic review, narrative reviews and mixed method reviews
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL and AMED. Studies will be restricted to English language only. No date restriction will be applied. Databases will be searched from their date of origin.
Review strategy	Studies will be evaluated to assess their relevance to the question asked and objective of review. The most relevant studies are those conducted in the UK, in the NHS settings, in the population of interest for the purpose of finding of what information is required by patients who had an experienced suspected drug allergy. Qualitative studies: Quality of studies will be evaluated on 3 key components • methodological quality (study limitations) • transferability (indirectness) • other considerations. The consistency of themes between various studies will also be evaluated. Thematic analysis will be conducted, and common themes across studies will be extracted and reported. The review will be considered as complete when no new themes are found within the area (theme saturation reached).

Component	Description
	For observational studies, surveys or audits the key findings will be summarised and presented. The overall review will take into account both the findings from the qualitative and quantitative studies. If information is not available, the review will be broadened to include: • adverse drug reactions (rather than just drug allergy) • information needs of those with general allergy • medical information for patients • the views and experience of healthcare professionals about patients' information needs.
Notes	When conducting the review; the following issues will be explored, with the focus on issues that could be addressed by provision of patient information and support: • What are the barriers and facilitators to optimal care for patients with drug allergy? • What is the patient perception of drug allergy? (This includes how much patients know about their allergy; are there any common misconceptions; what are the fears or anxieties?) • How the experience of 'drug allergy' (having symptoms, diagnosis, 'label' and management) impacts patients?

C.6 Non-specialist management – selective COX-2 inhibitors

Component	Description
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?
Objective	To establish whether, in clinical practice, it is possible to identify who can safely take a selective COX-2 inhibitor when they are allergic to NSAIDs, and if so, how this could be done
Population	Population: anyone with an allergy to one or more NSAIDs

Presence of factor or defining characteristics	• History of an allergy to more than one type of NSAID
	• 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	• RCTs • Prospective cohort studies • Case–control studies

Exclusions	Abstracts only Non-English papers
Review strategy	Ideally focus on studies with a multivariable analysis. Separately analyse the defining characteristic. Divide evidence by the type of selective COX-2 inhibitor that is used in the challenge test. Subgroup by people with a history of asthmatic or cutaneous reactions to NSAIDs.

C.7 Referral to specialist drug allergy services

C.7.1 Beta-lactam antibiotics

Component	Description
Review question	What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to beta-lactam antibiotics?
Objective	To investigate the clinical and cost effectiveness of referral for suspected allergy to beta-lactam antibiotics
Population	Patients presenting with suspected allergy to beta-lactam antibiotics Subgroups: • High antibiotic need • Age • Severity of reaction • People with suspected multiple antibiotic allergy
Interventions	Referral to specialist drug allergy services (for diagnosis, further investigations to identify safe alternatives or other management strategies)
Comparisons	No referral – management in primary care
Outcomes	For RCTs or comparative cohort studies: • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Inappropriate avoidance of drugs • Health-related quality of life
Study design	• RCTs – comparing referral versus no referral • Comparative observation studies
Exclusions	Non-English studies
How the information will be searched	Databases: Medline, Embase, CINHL Language: restrict to English only
The review strategy	Any special characteristics about the following which affect the study outcomes or applicability: • Population, type of drug allergy experienced, patients' age • Setting, speciality, who did the evaluation • Referral protocol and comparison • How outcomes were recorded

C.7.2 NSAIDs

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

Component	Description
Objective	To investigate the clinical and cost effectiveness of referral for suspected allergy to NSAIDs
Population	Patients presenting with suspected drug allergy to NSAIDs
Interventions	Referral to specialist drug allergy services (for diagnosis, further investigations to identify safe alternatives or other management strategies)
Comparisons	No referral – management in primary care
Outcomes	For RCTs or comparative cohort studies: • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Inappropriate avoidance of drugs • Health-related quality of life
Study design	• RCTs – comparing referral versus no referral • Comparative observation studies
Exclusions	Non-English studies
How the information will be searched	Databases: Medline, Embase, CINHL Language: restrict to English only
The review strategy	Any special characteristics about the following which affect the study outcomes or applicability: • Population, type of drug allergy experienced, patients' age • Setting, speciality or who did the evaluation • Referral protocol method and comparison • How outcomes are recorded

C.7.3 Local anaesthetics

Component	Description
Review question	What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to local anaesthetics?
Objective	To investigate the clinical and cost effectiveness of referral of suspected allergy to local anaesthetics
Population	Patients presenting with suspected drug allergy to local anaesthetics
Interventions	Referral to specialist drug allergy services (for diagnosis, further investigations to identify safe alternatives or other management strategies)
Comparisons	No referral – management in primary care
Outcomes	For RCTs or comparative cohort studies: • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Inappropriate avoidance of drugs • Health-related quality of life
Study design	• RCTs – comparing referral versus no referral • Comparative observation studies
Exclusions	Non-English studies
How the information will be searched	Databases: Medline, Embase, CINHL Language: restrict to English only

Component	Description
The review strategy	Any special characteristics about the following which affect the study outcomes or applicability: • Population, type of drug allergy experienced, patients' age • Setting, speciality or who did the evaluation • Referral protocol method and comparison • How outcomes are recorded

C.7.4 General anaesthesia

Component	Description
Review question	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?
Objective	To investigate the clinical and cost effectiveness of referral for suspected anaphylaxis due to drug allergy during general anaesthesia
Population	Patients presenting with an anaphylactic event due to suspected drug allergy during general anaesthesia
Interventions	Referral to specialist drug allergy services (for diagnosis, further investigations to identify safe alternatives or other management strategies)
Comparisons	No referral – management in primary care
Outcomes	For RCTs or comparative cohort studies: • Mortality • Number of repeat drug allergic reactions (including patient-reported episodes) • Length of hospital stay • Inappropriate avoidance of drugs • Health-related quality of life
Study design	• RCTs – comparing referral versus no referral • Comparative observation studies
Exclusions	Non-English studies
How the information will be searched	Databases: Medline, Embase, CINHL Language: restrict to English only
The review strategy	Any special characteristics about the following which affect the study outcomes or applicability: • Population, type of drug allergy experienced, patients' age • Setting, speciality or who did the evaluation • Referral protocol method and comparison • How outcomes are recorded

Appendix D: Economic review protocol

D.1 All review questions

Component	Description
Review question	All questions: health economic evidence
Objective	To identify economic evaluations relevant to the review questions set out above.
Criteria	• Populations, interventions and comparators must be as specified in the individual review protocols above. • Studies must be of a relevant economic study design (cost–utility analysis, cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be an abstract only, a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G.
Review strategy	Each study fulfilling the criteria above will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the NICE guidelines manual (2012).[77] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the GDG if required. The ultimate aim is to include studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the GDG if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded economic studies in Appendix I. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden) • OECD countries with predominantly private health insurance systems (for example,

	USA, Switzerland) • non-OECD settings (always 'Not applicable'). *Economic study type:* • cost–utility analysis • other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequence analysis) • comparative cost analysis • non-comparative cost analyses including cost-of-illness studies (always 'Not applicable'). *Year of analysis:* • The more recent the study, the more applicable it is. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix E: Clinical article selection

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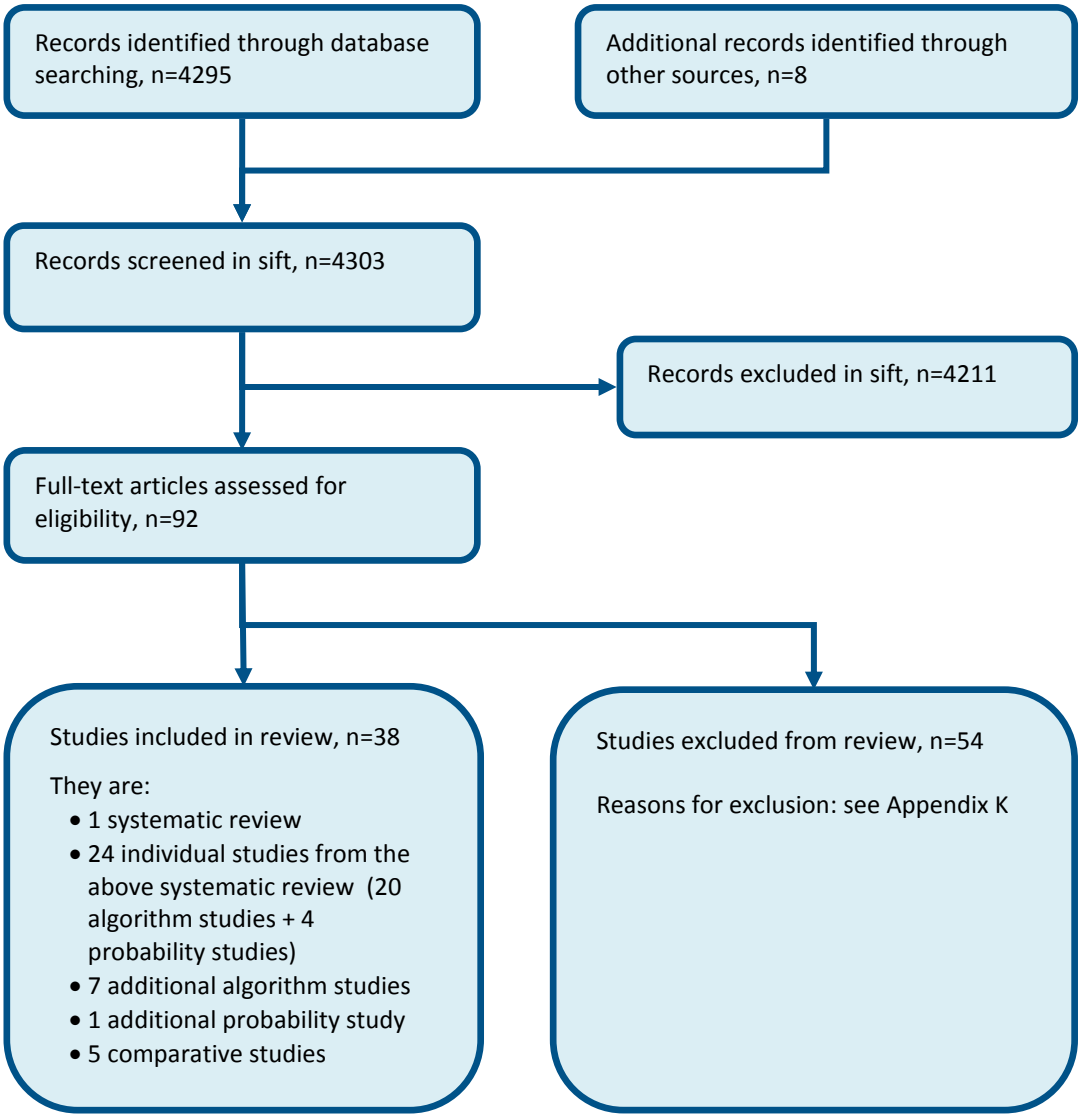
E.1 Assessment

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

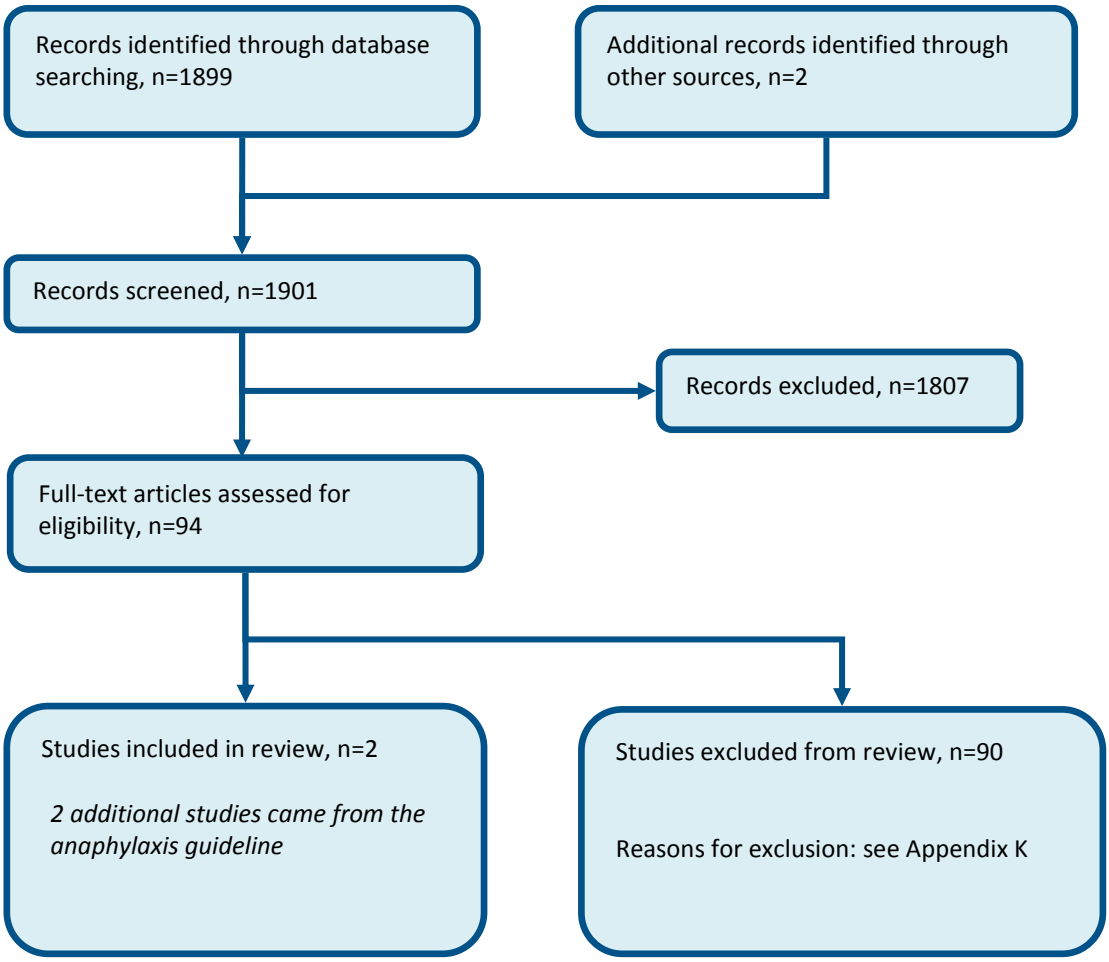
Figure 1: Flow chart of clinical article selection for the review of algorithms



E.2 Measuring serum tryptase after suspected anaphylaxis

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?

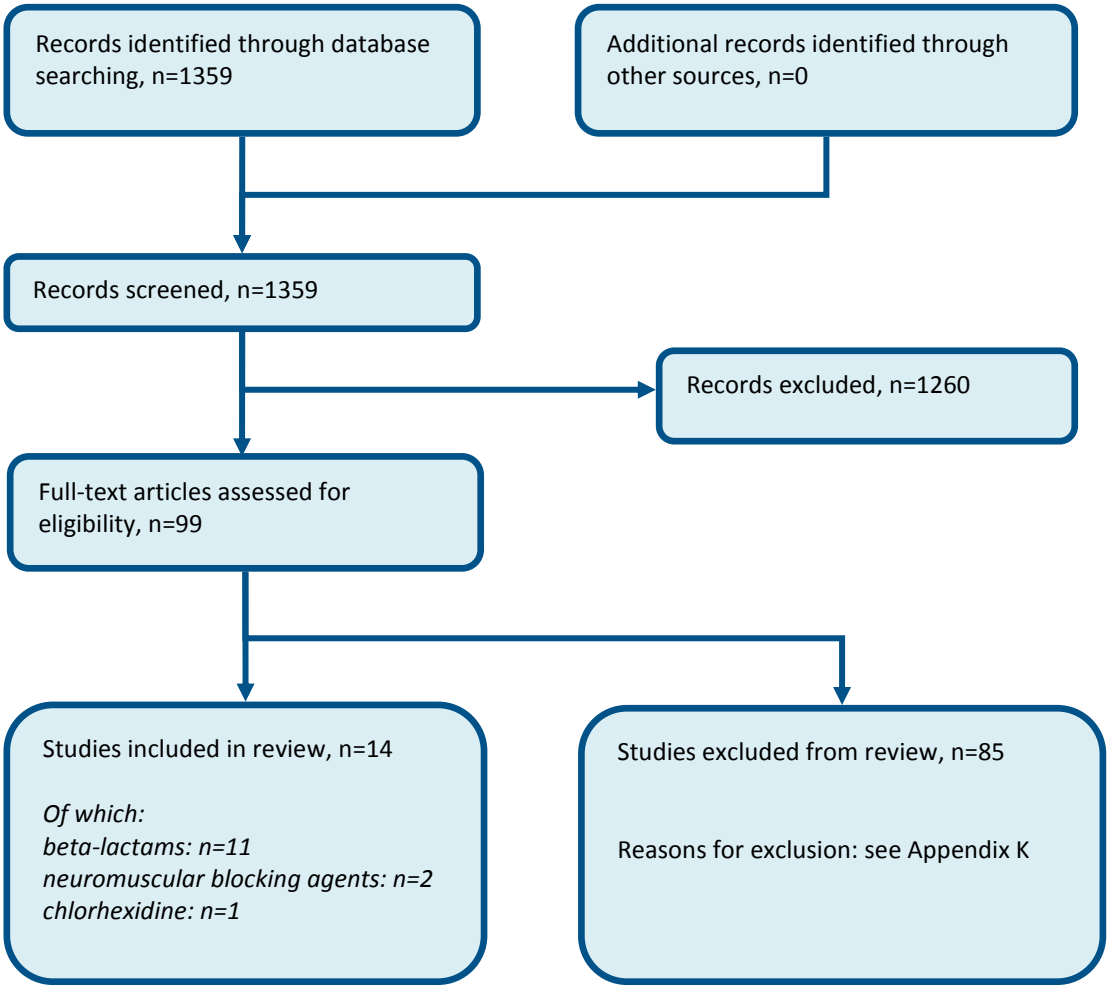
Figure 2: Flow chart of clinical article selection for the review of serum tryptase testing



E.3 Measuring serum specific IgE

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?

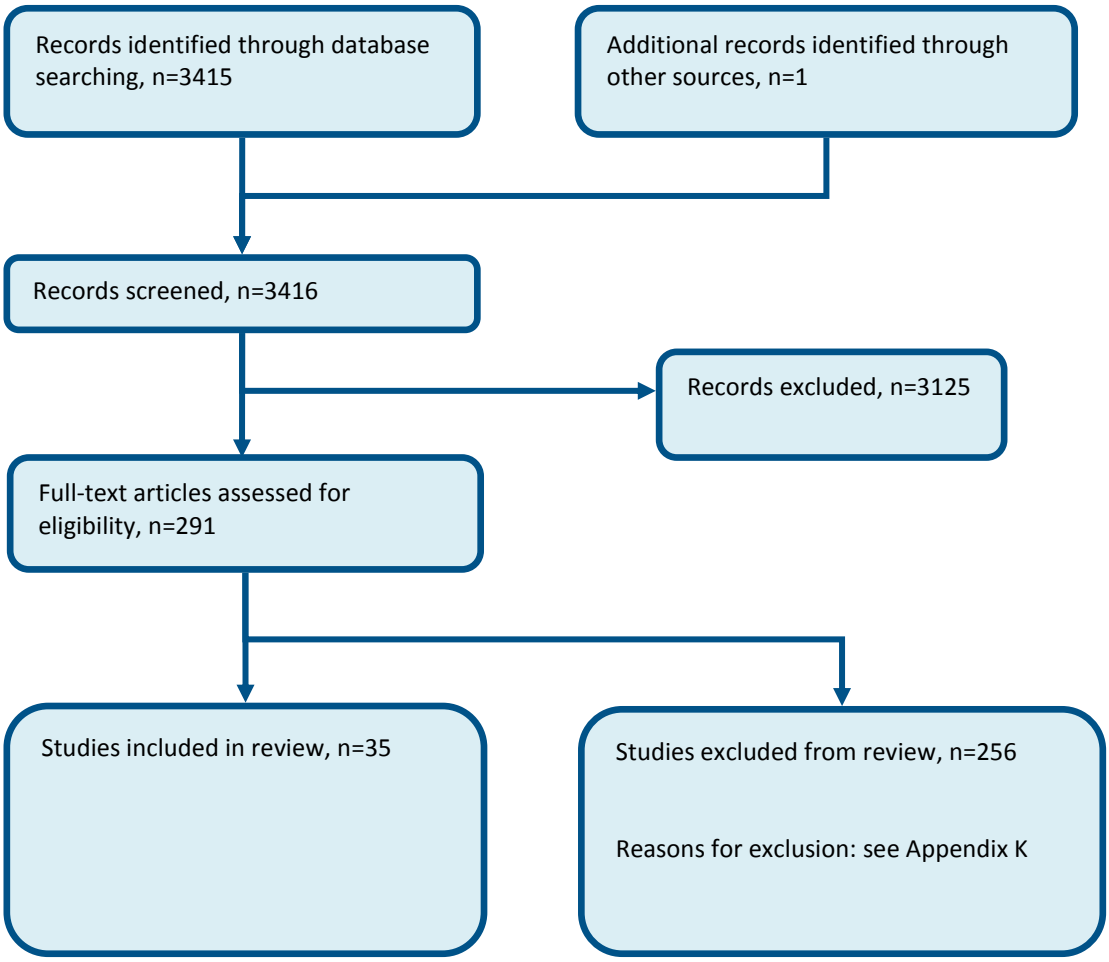
Figure 3: Flow chart of clinical article selection for the review of serum specific IgE testing



E.4 Documenting and sharing information with other healthcare professionals

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?

Figure 4: Flow diagram of clinical article selection for the review of documentation strategies

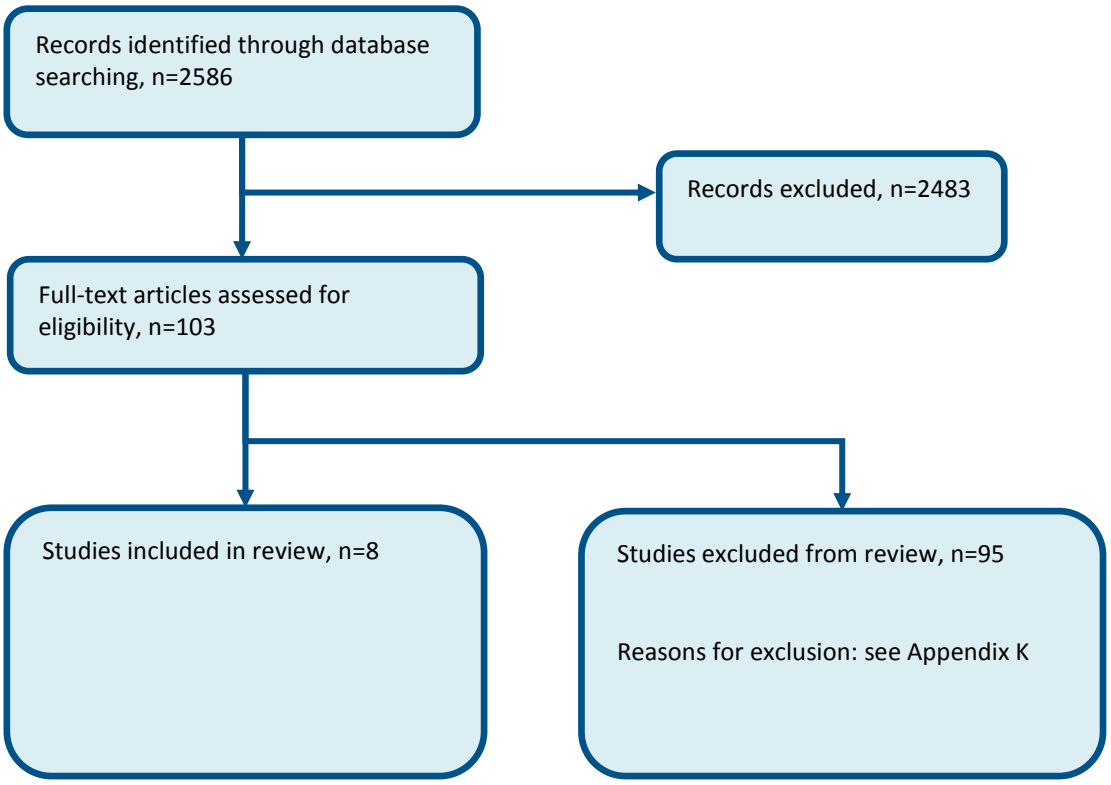


E.5 Providing information and support to patients

What information and support should individuals with suspected drug allergy or their parents or carers receive?

What information and support should individuals who have had specialist investigations or their parents or carers receive?

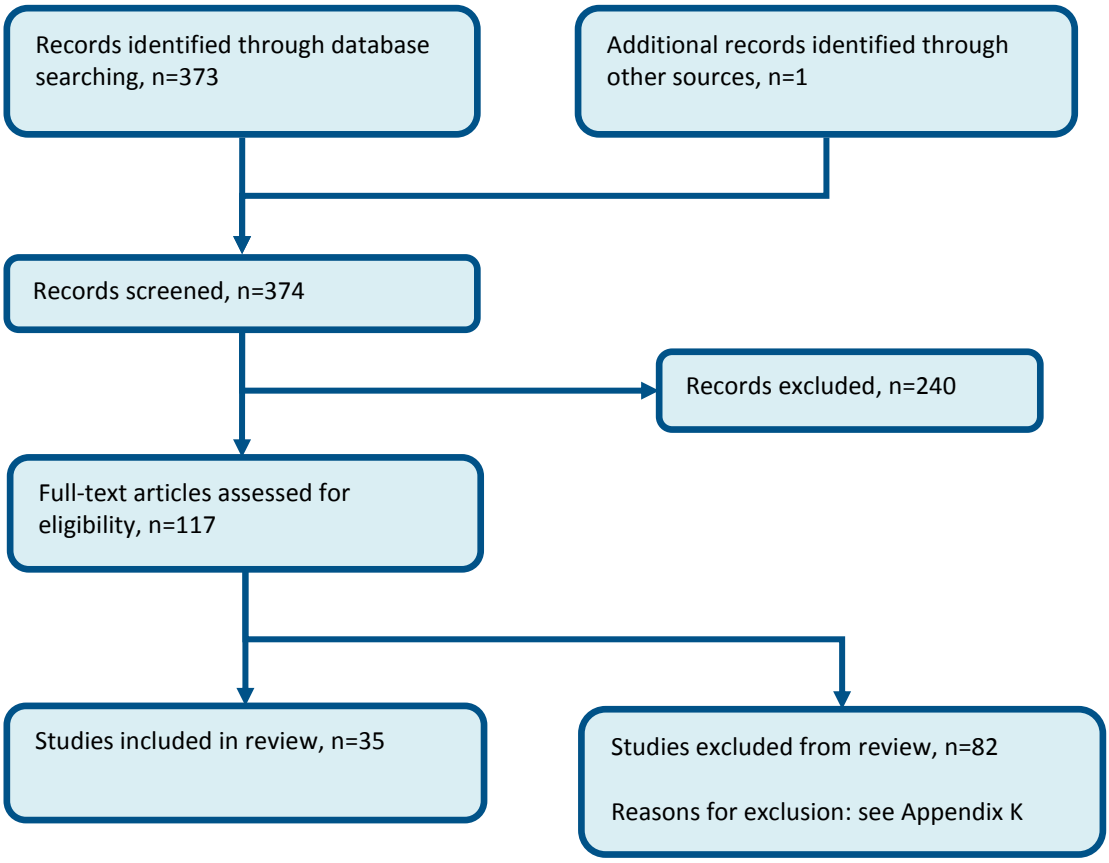
Figure 5: Flow chart of clinical article selection for the review of patient information and support



E.6 Non-specialist management – selective COX-2 inhibitors

In patients who have had an allergic reaction to NSAIDs what are the factors that indicate whether people can or cannot tolerate selective COX-2 inhibitors?

Figure 6: Flow chart of clinical article selection for the review of toleration of selective COX-2 inhibitors



E.7 Referral to specialist drug allergy services

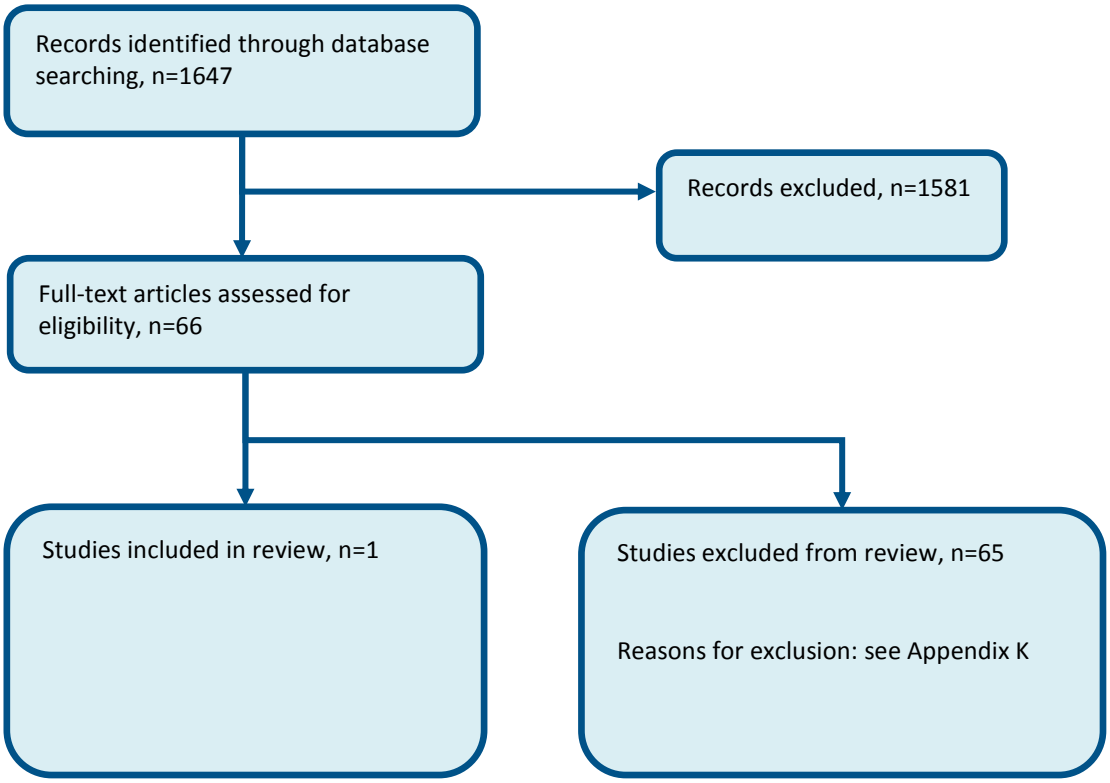
What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected allergy to beta-lactam antibiotics?

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 anaesthetics?

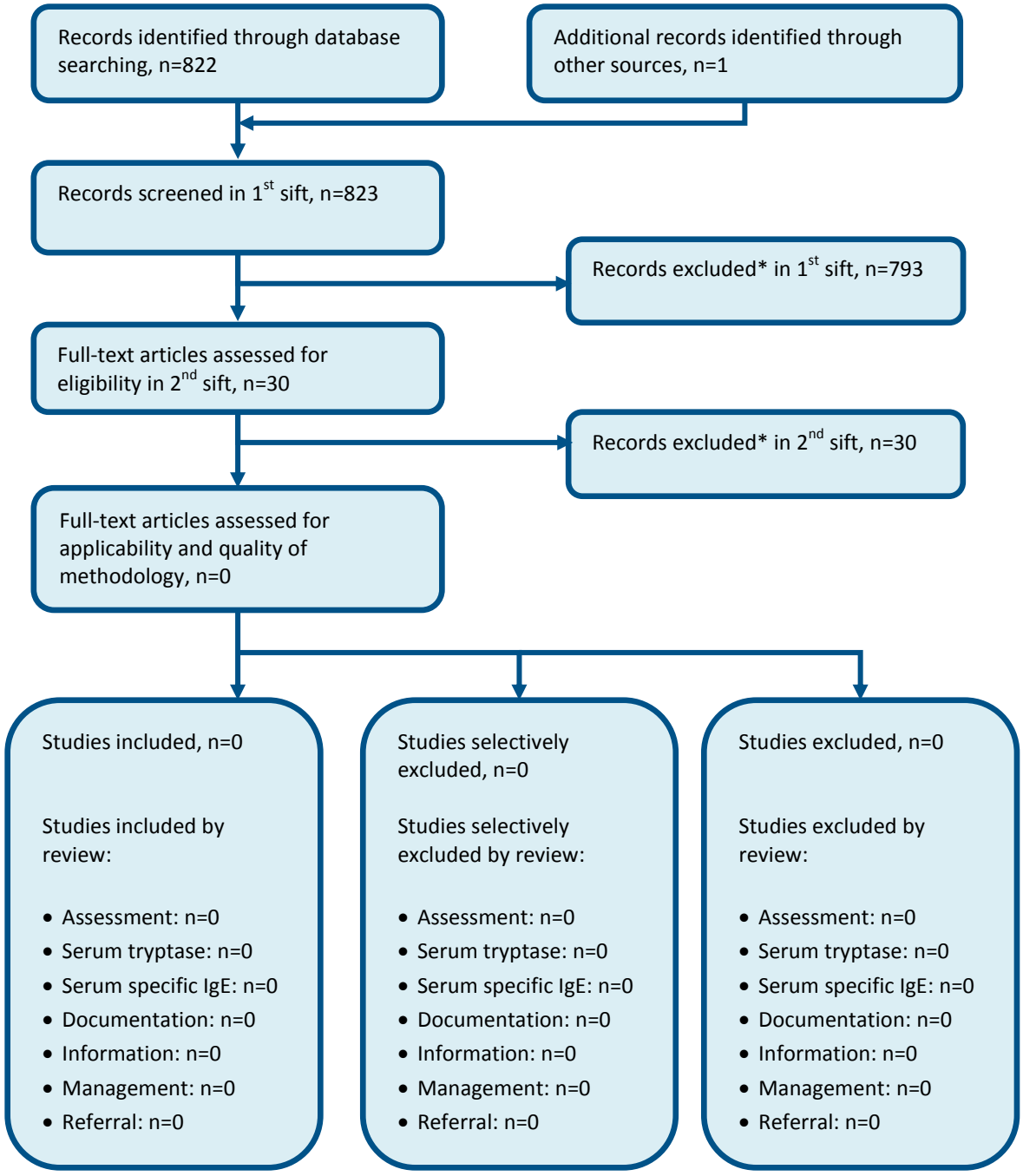
What is the clinical and cost effectiveness of referral to specialist drug allergy services for people with suspected anaphylaxis due to drug allergy during general anaesthesia?

Figure 7: Flow chart of clinical article selection for the review of referral to specialist drug allergy services



Appendix F: Economic article selection

Figure 8: Flow chart of economic article selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G: Literature search strategies

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G.3 Health economics search 63

Search strategies used for the drug allergy guideline are outlined below and were run in accordance with the methodology in the NICE Guidelines Manual 2012.[77] All clinical searches were run up to **10 January 2014**, and **health economic searches up to 15 January 2014**. Any studies added to the databases after this date were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English unless otherwise stated.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Usually, searches were constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search Filters were also added to the search where appropriate.

Searches for **the information and support review** were run in Medline (OVID), Embase (OVID) and Cinahl (EBSCO). Searches were constructed by combining population terms, patient information or patient views terms and qualitative study filter.

Searches for the **health economic reviews** were run in Medline (OVID), Embase (OVID), the NHS Economic Evaluations Database (NHS EED), the Health Technology Assessment (HTA) database and the Health Economic Evaluation Database (HEED). Searches in NHS EED and HEED were constructed only using population terms. For Medline and Embase an economic filter (instead of a study type filter) was combined with the population terms.

G.1 Study filter search terms

G.1.1 Systematic review search terms

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/
3.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4.	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
4.	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or

	cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

G.1.2 Randomised controlled studies (RCTs) search terms

Medline search terms

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ab.
4.	placebo.ab.
5.	randomly.ab.
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	Randomized controlled trial/
2.	Crossover procedure/
3.	Single blind procedure/
4.	Double blind procedure/
5.	random*.ti,ab.
6.	factorial*.ti,ab.
7.	(crossover* or cross over* or cross-over*).ti,ab.
8.	((doubl* or singl*) adj blind*).ti,ab.
9.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
10.	or/1-9

G.1.3 Diagnostic accuracy search terms

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(ROC curve* or AUC).ti,ab.
8.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.

4.	(predictive value* or PPV or NPV).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(ROC curve* or AUC).ti,ab.
7.	(diagnos* adj2 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

G.1.4 Observational studies search terms

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	cross sectional.ti,ab.
10.	or/1-9

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or case control or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) adj3 (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-15

G.1.5 Qualitative studies and surveys search terms

Medline search terms

1	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
2	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4	or/1-3

Embase search terms

1	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
2	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4	or/1-3

Cinahl search terms

S1	(MH "Qualitative Studies+")
S2	(MH "Qualitative Validity+")
S3	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S4	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S5	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S6	S1 or S2 or S3 or S4 or S5

G.1.6 Excluded studies

The following publication types and animal studies were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/

13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	exp animal/ not human/
10.	nonhuman/
11.	exp experimental animal/
12.	exp animal experiment/
13.	exp animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

G.2 Searches for specific questions

G.2.1 Assessment

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

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy	Algorithms, protocols or probability scores		Not limited to specific study designs.	All years to 10/01/2014 English only Exclusion filter applied

Medline search terms

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	hypersensitivity/

5	exp drug toxicity/
6	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
7	or/3-6
8	algorithms/
9	clinical protocols/
10	critical pathways/
11	algorithm*.ti,ab.
12	*decision trees/
13	*decision support techniques/
14	((probablilit* or predict*) adj (scor* or rule*)).ti,ab.
15	((decision or diagnostic) adj (rule or rules)).ti,ab.
16	scor* system*.ti,ab.
17	exp *causality/
18	(causalit* or causation*).ti,ab.
19	((protocol* or path* or plan* or pattern*) adj3 (patient* or clinical* or critical*)).ti,ab.
20	or/8-19
21	7 and 20

1 **Embase search terms**

1	exp *drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	*hypersensitivity/ or *allergic reaction/
5	exp *drug eruption/
6	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
7	or/3-6
8	exp *algorithm/
9	*clinical protocol/
10	*clinical pathway/
11	algorithm*.ti,ab.
12	*"decision tree"/
13	*decision support system/
14	*scoring system/
15	((probablilit* or predict*) adj (scor* or rule*)).ti,ab.
16	((decision or diagnostic) adj (rule or rules)).ti,ab.
17	scor* system*.ti,ab.
18	(causalit* or causation*).ti,ab.
19	((protocol* or path* or plan* or pattern*) adj3 (patient* or clinical* or critical*)).ti,ab.
20	or/8-19
21	7 and 20

2 **Cochrane search terms**

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID*

	or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Drug Toxicity] explode all trees
#5	((adverse near/3 (reaction* or effect* or event*)) near/3 drug*):ti,ab
#6	#3 or #4 or #5
#7	[mh ^Algorithms]
#8	[mh ^"Clinical Protocols"]
#9	[mh ^"Critical Pathways"]
#10	algorithm*:ti,ab
#11	((protocol* or path* or plan* or pattern*) near/3 (patient* or clinical* or critical*)):ti,ab
#12	[mh ^"Decision Trees"]
#13	[mh ^"Decision Support Techniques"]
#14	((probablilit* or predict*) next (scor* or rule*)):ti,ab
#15	((decision or diagnostic) next (rule or rules)):ti,ab
#16	scor* system*:ti,ab
#17	[mh ^causality]
#18	(causalit* or causation*):ti,ab
#19	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20	#6 and #19

G.2.2 Measuring serum tryptase after suspected anaphylaxis

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?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy, anaphylaxis or indicators of anaphylaxis terms	Tryptase terms		RCTs, diagnostic accuracy, observational studies, systematic reviews (Medline and Embase only)	All years to 10/01/2014 All languages Exclusion filter applied

Medline search terms

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	exp drug toxicity/
5	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
6	anaphylaxis/
7	anaphyl*.ti,ab.
8	exp airway obstruction/

9	((airway* or lung* or pulmonary or respirat* or bronch* or trach*) adj2 (obstruct* or block*)).ti,ab.
10	exp hypotension/
11	(hypotension or low blood pressure).ti,ab.
12	((severe or serious) adj2 (cutaneous or skin or dermat*)).ti,ab.
13	or/3-12
14	tryptases/
15	tryptase*.ti,ab.
16	((serum* or mastcell*or mast-cell* or mast cell*) adj3 (test* or biops* or assay* or exam*)).tw.
17	or/14-16
18	13 and 17

1 **Embase search terms**

1	exp drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	exp adverse drug reaction/
5	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
6	serum sickness/
7	anaphylaxis/
8	anaphylactic shock/
9	anaphyl*.ti,ab.
10	airway constriction/ or airway obstruction/ or bronchus obstruction/ or trachea obstruction/ or trachea stenosis/ or upper respiratory tract obstruction/
11	((airway* or lung* or pulmonary or respirat* or bronch* or trach*) adj2 (obstruct* or block*)).ti,ab.
12	exp hypotension/
13	(hypotension or low blood pressure).ti,ab.
14	((severe or serious) adj2 (cutaneous or skin or dermat*)).ti,ab.
15	or/3-14
16	tryptase/
17	tryptase*.ti,ab.
18	((serum* or mastcell*or mast-cell* or mast cell*) adj3 (test* or biops* or assay* or exam*)).tw.
19	or/16-18
20	15 and 19

2 **Cochrane search terms**

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2

#4	MeSH descriptor: [Drug Toxicity] explode all trees
#5	(adverse near/3 (reaction* or effect* or event*) near/3 drug*):ti,ab
#6	MeSH descriptor: [Anaphylaxis] explode all trees
#7	anaphyl*:ti,ab
#8	MeSH descriptor: [Airway Obstruction] explode all trees
#9	((airway* or lung* or pulmonary or respirat* or bronch* or trach*) near/2 (obstruct* or block*)):ti,ab
#10	MeSH descriptor: [Hypotension] explode all trees
#11	(hypotension or low blood pressure):ti,ab
#12	((severe or serious) near/2 (cutaneous or skin or dermat*)):ti,ab
#13	#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	MeSH descriptor: [Tryptases] this term only
#15	tryptase*:ti,ab
#16	((serum* or mastcell*or mast-cell* or mast cell*) near/3 (test* or biops* or assay* or exam*)):ti,ab
#17	#14 or #15 or #16
#18	#13 and #17

G.2.3 Measuring serum specific IgE

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 or suxamethonium?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy or specific penicillin terms	IgE terms		RCTs, diagnostic accuracy, observational studies, systematic reviews (Medline and Embase only)	All years to 10/01/2014 All languages Exclusion filter applied

Medline search terms

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	(penicillin g or penicillin v or ampicillin or amoxicillin or cefaclor or suxamethomium or chlorhexidine or morphine).mp.
5	or/3-4
6	exp immunoglobulin E/
7	((serum specific or IgE or immunoglobulin E or radioallergosorbent or allerg*) adj3 (test* or assess*)).ti,ab.
8	or/6-7
9	5 and 8

Embase search terms

1	exp drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	(penicillin g or penicillin v or ampicillin or amoxicillin or cefaclor or suxamethomium or chlorhexidine or morphine).mp.
5	or/3-4
6	immunoglobulin E/
7	((serum specific or IgE or immunoglobulin E or radioallergosorbent or allerg*) adj3 (test* or assess*)).ti,ab.
8	or/6-7
9	5 and 8

Cochrane search terms

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2
4	(penicillin g or penicillin v or ampicillin or amoxicillin or cefaclor or suxamethomium or chlorhexidine or morphine)
5	#3 or #4
6	MeSH descriptor: [Immunoglobulin E] explode all trees
7	((serum specific or IgE or immunoglobulin E or radioallergosorbent or allerg*) near/3 (test* or assess*)):ti,ab
8	#6 or #7
9	#5 and #8

G.2.4 Documenting and sharing information with other healthcare professionals

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?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy or adverse drug reaction terms	Documentation or communication terms		Not limited to specific study design	All years to 10/01/2014 English only Exclusion filter applied

Medline search terms

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or

	intolerance)).ti,ab.
3	or/1-2
4	exp drug toxicity/
5	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
6	or/3-5
7	documentation/
8	exp "forms and records control"/ or clinical coding/
9	medical records/ or medical record linkage/ or medical records, problem-oriented/ or medical records systems, computerized/ or electronic health records/
10	information systems/ or medication systems/ or medication reconciliation/ or medication systems, hospital/ or clinical laboratory information systems/ or clinical pharmacy information systems/ or hospital information systems/ or medical order entry systems/ or operating room information systems/
11	medical informatics applications/ or decision making, computer-assisted/ or therapy, computer-assisted/ or drug therapy, computer-assisted/
12	decision support systems, clinical/
13	patient identification systems/ or radio frequency identification device/
14	electronic prescribing/
15	reminder systems/
16	data display/
17	exp clinical audit/
18	((document* or record* or notes) adj3 allerg*).ti,ab.
19	(barcode* or bar code* or wristband* or wrist band* or armband* or arm band* or pendant* or bracelet* or necklace*).ti,ab.
20	(((computer* or electronic*) adj3 (decision* or tool* or support* or prescri*)) or eprescri* or e-prescri*).ti,ab.
21	((computer* adj3 order entry) or CPOE).ti,ab.
22	((clinical support or decision support) adj3 system*).ti,ab.
23	((drug* or medic* or safety) adj3 (alert* or warn* or message*)).ti,ab.
24	summary of care record*.ti,ab.
25	(patient* adj3 (held or hold* or access*) adj3 (record* or note*)).ti,ab.
26	((medical record* or patient* record* or medical note* or patient* note* or drug* chart*) adj3 (design or layout or template*)).ti,ab.
27	((audit or audits or audited or auditing) adj4 (effect* or efficacy or valid*)).ti,ab.
28	or/7-27
29	6 and 28

1 **Embase search terms**

1	exp *drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	exp *drug eruption/
5	*adverse drug reaction/
6	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
7	or/3-6

8	documentation/ or medical documentation/ or medical order/ or medical record/ or electronic medical record/
9	coding/ or "coding and classification"/ or patient coding/
10	information system/ or computerized provider order entry/ or electronic prescribing/ or decision support system/ or hospital information system/ or medical information system/ or nursing information system/ or reminder system/ or computer system/
11	medical informatics/
12	computer assisted therapy/ or computer assisted drug therapy/
13	patient identification/
14	medical audit/
15	((document* or record* or notes) adj3 allerg*).ti,ab.
16	(barcode* or bar code* or wristband* or wrist band* or armband* or arm band* or pendant* or bracelet* or necklace*).ti,ab.
17	(((computer* or electronic*) adj3 (decision* or tool* or support* or prescri*)) or eprescri* or e-prescri*).ti,ab.
18	((computer* adj3 order entry) or CPOE).ti,ab.
19	((clinical support or decision support) adj3 system*).ti,ab.
20	((drug* or medic* or safety) adj3 (alert* or warn* or message*)).ti,ab.
21	summary of care record*.ti,ab.
22	(patient* adj3 (held or hold* or access*) adj3 (record* or note*)).ti,ab.
23	((medical record* or patient* record* or medical note* or patient* note* or drug* chart*) adj3 (design or layout or template*)).ti,ab.
24	((audit or audits or audited or auditing) adj4 (effect* or efficacy or valid*)).ti,ab.
25	or/8-24
26	7 and 25

1 **Cochrane search terms**

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Drug Toxicity] explode all trees
#5	(adverse near/3 (reaction* or effect* or event*) near/3 drug*):ti,ab
#6	#3 or #4 or #5
#7	MeSH descriptor: [Documentation] this term only
#8	MeSH descriptor: [Forms and Records Control] explode all trees
#9	MeSH descriptor: [Clinical Coding] this term only
#10	MeSH descriptor: [Medical Records] this term only
#11	MeSH descriptor: [Medical Record Linkage] this term only
#12	MeSH descriptor: [Medical Records, Problem-Oriented] this term only
#13	MeSH descriptor: [Medical Records Systems, Computerized] explode all trees
#14	MeSH descriptor: [Electronic Health Records] this term only
#15	MeSH descriptor: [Information Systems] this term only
#16	MeSH descriptor: [Medication Systems] explode all trees
#17	MeSH descriptor: [Medication Reconciliation] explode all trees

#18	MeSH descriptor: [Medication Systems, Hospital] this term only
#19	MeSH descriptor: [Clinical Laboratory Information Systems] this term only
#20	MeSH descriptor: [Clinical Pharmacy Information Systems] this term only
#21	MeSH descriptor: [Hospital Information Systems] this term only
#22	MeSH descriptor: [Medical Order Entry Systems] this term only
#23	MeSH descriptor: [Operating Room Information Systems] explode all trees
#24	MeSH descriptor: [Medical Informatics Applications] explode all trees
#25	MeSH descriptor: [Decision Making, Computer-Assisted] this term only
#26	MeSH descriptor: [Therapy, Computer-Assisted] this term only
#27	MeSH descriptor: [Drug Therapy, Computer-Assisted] this term only
#28	MeSH descriptor: [Decision Support Systems, Clinical] this term only
#29	MeSH descriptor: [Patient Identification Systems] explode all trees
#30	MeSH descriptor: [Electronic Prescribing] this term only
#31	MeSH descriptor: [Reminder Systems] this term only
#32	MeSH descriptor: [Data Display] this term only
#33	MeSH descriptor: [Clinical Audit] explode all trees
#34	((document* or record* or notes) near/3 allerg*):ti,ab
#35	(barcode* or bar code* or wristband* or wrist band* or armband* or arm band* or pendant* or bracelet* or necklace*):ti,ab
#36	(((computer* or electronic*) near/3 (decision* or tool* or support* or prescri*)) or eprescri* or e-prescri*):ti,ab
#37	((computer* near/3 order entry) or CPOE):ti,ab
#38	((clinical support or decision support) near/3 system*):ti,ab
#39	((drug* or medic* or safety) near/3 (alert* or warn* or message*)):ti,ab
#40	summary of care record*:ti,ab
#41	((patient* record* or patient* note*) near/3 (held or hold* or access*)):ti,ab
#42	((medical record* or patient* record* or medical note* or patient* note* or drug* chart*) near/3 (design or layout or template*)):ti,ab
#43	((audit or audits or audited or auditing) near/4 (effect* or efficacy or valid*)):ti,ab
#44	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43
#45	#6 and #44

G.2.5 Providing information and support to patients

What information and support should individuals with suspected drug allergy or their parents or carers receive?

What information and support should individuals who have had specialist investigations or their parents or carers receive?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy or adverse drug reaction terms	Patient information terms		Qualitative literature	All years to 10/01/2014 English only Exclusion filter applied

1 **Medline search terms**

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	hypersensitivity/
5	exp drug toxicity/
6	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
7	or/3-6
8	patients/ or inpatients/ or outpatients/
9	caregivers/ or exp family/ or exp parents/ or exp legal-guardians/
10	(patient* or carer* or famil*).ti,ab.
11	or/8-10
12	Popular works publication type/ or exp information services/ or publications/ or books/ or pamphlets/ or counseling/ or directive counseling/
13	11 and 12
14	(patient* adj3 (education or educate or educating or literature or leaflet* or booklet* or pamphlet* or information)).ti,ab.
15	patient education as topic/
16	consumer health information/
17	(information* adj3 (patient* or need* or requirement* or support* or seek* or access* or disseminat* or barrier*)).ti,ab.
18	(discharge* adj3 (information* or advice)).ti,ab.
19	or/13-18
20	exp consumer-satisfaction/ or personal-satisfaction/ or exp patient-acceptance-of-health-care/
21	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform*)).ti,ab.
22	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (knowledge or awareness or misconception* or understanding or misunderstanding)).ti,ab.
23	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (experience or experiences or opinion* or concern* or belief* or feeling* or idea* or satisfaction or anxiet* or fear* or acceptance or denial or stigma* or label* or behaviour* or behavior*)).ti,ab.
24	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (need* or requirement* or support* or communication* or involvement)).ti,ab.
25	or/20-24
26	19 or 25
27	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
28	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
29	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
30	or/27-29
31	7 and 26 and 30

1 **Embase search terms**

1	exp drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	hypersensitivity/ or allergic reaction/
5	exp drug eruption/
6	adverse drug reaction/
7	(adverse adj3 drug* adj3 (reaction* or effect* or event*)).ti,ab.
8	or/3-7
9	patient/ or hospital patient/ or outpatient/
10	caregiver/ or exp family/ or exp parent/
11	(patient* or carer* or famil*).ti,ab.
12	or/9-11
13	information service/ or information center/ or publication/ or book/ or counseling/ or directive counseling/
14	12 and 13
15	patient attitude/ or patient preference/ or patient satisfaction/ or consumer attitude/
16	patient information/ or consumer health information/
17	patient education/
18	(patient* adj3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet*)).ti,ab.
19	(information* adj3 (need* or requirement* or support* or seek* or access* or disseminat* or barrier*)).ti,ab.
20	(discharge* adj3 (information* or advice)).ti,ab.
21	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform*)).ti,ab.
22	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (knowledge or awareness or misconception* or understanding or misunderstanding)).ti,ab.
23	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (experience or experiences or opinion* or concern* or belief* or feeling* or idea* or satisfaction or anxiet* or fear* or acceptance or denial or stigma* or label* or behaviour* or behavior*)).ti,ab.
24	((patient* or user* or carer* or famil* or parent* or father* or mother*) adj3 (need* or requirement* or support* or communication* or involvement)).ti,ab.
25	or/14-24
26	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
27	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
28	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
29	or/26-28
30	8 and 25 and 29

2 **Cinahl search terms**

S1	(MH "Drug Hypersensitivity+")
S2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) n1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) n2 (allerg* or hypersensitivity or senstivity or intolerance))
S3	S1 or S2
S4	(MH "Hypersensitivity")
S5	(MH "Drug Toxicity+")
S6	(adverse n3 drug* n3 (reaction* or effect* or event*))
S7	S3 or S4 or S5 or S6
S8	MH Patients or MH Inpatients or MH Outpatients or MH Caregivers or MH Family+ or MH Parents+ or MH Guardianship, Legal or patients or carer* or famil*
S9	MH Information Services+ or MH Books+ or MH Pamphlets or MH Counseling
S10	S8 and S9
S11	MH Patient Education+ or MH Consumer Health Information
S12	(patient* n3 (education or educate or educating or information or literature or leaflet* or booklet* or pamphlet*))
S13	((patient* or user* or carer* or famil* or parent* or father* or mother*) n3 (attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or inform or knowledge or awareness or misconception* or understanding or misunderstanding or experience or experiences or opinion* or concern* or belief* or feeling* or idea* or satisfaction or anxiet* or fear* or acceptance or denial or stigma* or label* or behaviour* or behavior* or need* or requirement* or support* or communication* or involvement))
S14	MH Consumer Satisfaction+ or MH Consumer Attitudes or MH Personal Satisfaction
S15	(MH "Patient Attitudes") OR (MH "Family Attitudes+")
S16	(information* n3 (need* or requirement* or support* or seek* or access* or disseminat* or barrier*))
S17	(discharge* n3 (information* or advice))
S18	S11 or S12 or S13 or S14 or S15 or S16 or S17
S19	(MH "Qualitative Studies+")
S20	(MH "Qualitative Validity+")
S21	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S22	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S23	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S24	S19 or S20 or S21 or S22 or S23
S25	S7 and S18 and S25

G.2.6 Non-specialist management – selective COX-2 inhibitors

In patients who have had an allergic reaction to NSAIDs what are the factors that indicate whether people can or cannot tolerate selective COX-2 inhibitors?

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy terms	COX-2 terms	Other NSAID terms	Not limited to specific study design	All years to 10/01/2014 English only Exclusion filter applied

1 **Medline search terms**

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	hypersensitivity/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5	exp drug toxicity/
6	or/3-5
7	exp cyclooxygenase 2 inhibitors/
8	(((cyclooxygenase 2 or cyclooxygenase II or cox 2 or cox II) adj inhibitor*) or coxib*).ti,ab.
9	(apricoxib or celecoxib or celebrex or cimicoxib or deracoxib or etoricoxib or firocoxib or flosulide or iguratimod or lumiracoxib or mavacoxib or meloxicam or nimesulide or parecoxib or robenacoxib or rofecoxib or tilmacoxib or valdecoxib).mp.
10	or/7-9
11	anti-inflammatory agents, non-steroidal/
12	(NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory))).ti,ab.
13	or/11-12
14	6 and 10 and 13

2 **Embase search terms**

1	exp *drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	*hypersensitivity/ or *allergic reaction/
5	exp *drug eruption/
6	or/3-5
7	exp cyclooxygenase 2 inhibitor/
8	(((cyclooxygenase 2 or cyclooxygenase II or cox 2 or cox II) adj inhibitor*) or coxib*).ti,ab.
9	(apricoxib or bardoxolone or bardoxolone methyl or celecoxib or celebrex or cimicoxib or darbufelone or deracoxib or etoricoxib or firocoxib or flosulide or iguratimod or lumiracoxib or mavacoxib or meloxicam or nimesulide or parecoxib or robenacoxib or rofecoxib or tilmacoxib or valdecoxib or vedaprofen).mp.
10	or/7-9
11	nonsteroid antiinflammatory agent/
12	(NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory))).ti,ab.
13	or/11-12

14	6 and 10 and 13

Cochrane search terms

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2
#4	MeSH descriptor: [Hypersensitivity] this term only
#5	MeSH descriptor: [Hypersensitivity, Delayed] explode all trees
#6	MeSH descriptor: [Hypersensitivity, Immediate] explode all trees
#7	MeSH descriptor: [Drug Toxicity] explode all trees
#8	#3 or #4 or #5 or #6 or #7
#9	MeSH descriptor: [Cyclooxygenase 2 Inhibitors] explode all trees
#10	(((cyclooxygenase 2 or cyclooxygenase II or cox 2 or cox II) near/1 inhibitor*) or coxib*):ti,ab
#11	(apricoxib or celecoxib or celebrex or cimicoxib or deracoxib or etoricoxib or firocoxib or flosulide or iguratimod or lumiracoxib or mavacoxib or meloxicam or nimesulide or parecoxib or robenacoxib or rofecoxib or tilmacoxib or valdecoxib):ti,ab,kw
#12	#9 or #10 or #11
#13	MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] this term only
#14	(NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory))):ti,ab
#15	#13 or #14
#16	#8 and #12 and #15

G.2.7 Referral to specialist drug allergy services

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

Search constructed by combining the columns in the following table using the AND Boolean operator. Exclusion filter applied using NOT Boolean operator

Population	Intervention or exposure	Comparison	Study design filters	Date parameters and other limits
Drug allergy terms	Referral or specialist care terms		Not limited to specific study design	All years to 10/01/2014 English only Exclusion filter applied

Medline search terms

1	exp drug hypersensitivity/
2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or

	antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3	or/1-2
4	(refer or referred or referral*).ti,ab.
5	(allerg* adj2 (service or clinic* or hospital* or centre* or center* or specialist* or physician* or doctor*)).ti,ab.
6	(specialist* adj2 (service* or clinic* or hospital* or centre* or center* or physician or doctor)).ti,ab.
7	allergist*.ti,ab.
8	specialization/
9	or/4-8
10	3 and 9

1 **Embase search terms**

1	exp drug hypersensitivity/
2	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3	or/1-2
4	(refer or referred or referral*).ti,ab.
5	(allerg* adj2 (service or clinic* or hospital* or centre* or center* or specialist* or physician* or doctor*)).ti,ab.
6	(specialist* adj2 (service* or clinic* or hospital* or centre* or center* or physician or doctor)).ti,ab.
7	allergist*.ti,ab.
8	medical specialist/
9	or/4-8
10	3 and 9

2 **Cochrane search terms**

#1	MeSH descriptor: [Drug Hypersensitivity] explode all trees
#2	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) near/1 (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) near/3 (allerg* or hypersensitivit* or sensitivit* or intolerance)):ti,ab
#3	#1 or #2
#4	(refer or referred or referral*):ti,ab
#5	(allerg* near/2 (service or clinic* or hospital* or centre* or center* or specialist* or physician* or doctor*)):ti,ab
#6	(specialist* near/2 (service* or clinic* or hospital* or centre* or center* or physician or doctor)):ti,ab
#7	allergist*:ti,ab
#8	MeSH descriptor: [Specialization] explode all trees
#9	#4 or #5 or #6 or #7 or #8
#10	#3 and #9

G.3 Health economics search

Economic searches were conducted in Medline, Embase, HEED and CRD for NHS EED and HTA.

Population	Intervention or exposure	Comparison	Study filter used	Date parameters and other limits
Drug allergy			Economic (Medline and Embase only)	Medline and Embase 2011 to 15/01/2014 CRD EED and HTA all years to 15/01/2014 All languages

CRD search terms

1	MeSH DESCRIPTOR Drug Hypersensitivity EXPLODE ALL TREES
2	(((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)))
3	1 or 2

HEED search terms

1	ax= 'drug allergy' within 2
2	ax= 'drug allergies' within 2
3	ax= 'drugs allergy' within 2
4	ax= 'medicine allergy' within 2
5	ax= 'medicine allergies' within 2
6	ax= 'medicines allergy' within 2
7	ax= 'medication allergy' within 2
8	ax= 'medication allergies' within 2
9	ax= 'medications allergy' within 3
10	ax= 'penicillin allergy' within 2
11	ax= 'penicillin allergies' within 2
12	ax= 'penicillins allergy' within 2
13	ax= 'beta-lactums allergy' within 2
14	ax= 'NSAIDs allergy' within 2
15	ax= 'Non-steroidal antinflammatory drugs allergy' within 2
16	ax= 'Non-steroidal anti-inflammatory drugs allergy' within 2
17	ax= 'Non-steroidal antiinflammatory drugs allergy' within 2
18	ax= 'drug allergic' within 2
19	ax= 'anaesthesia allergy' within 2
20	ax= 'anesthesia allergy' within 2
21	ax= 'anaesthetic allergy' within 2
22	ax= 'anaesthetics allergy' within 2
23	ax= 'anesthetic allergy' within 2
24	ax= 'anesthetics allergy' within 2
25	cs= 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

1 **Medline search terms**

1.	exp drug hypersensitivity/
2.	((drug* or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj3 (allerg* or hypersensitivit* or sensitivit* or intolerance)).ti,ab.
3.	or/1-2
4.	economics/
5.	value of life/
6.	exp "costs and cost analysis"/
7.	exp economics, hospital/
8.	exp economics, medical/
9.	economics, nursing/
10.	economics, pharmaceutical/
11.	exp "fees and charges"/
12.	exp budgets/
13.	budget*.ti,ab.
14.	cost*.ti.
15.	(economic* or pharmaco?economic*).ti.
16.	(price* or pricing*).ti,ab.
17.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
18.	(financ* or fee or fees).ti,ab.
19.	(value adj2 (money or monetary)).ti,ab.
20.	or/4-19
21.	exp models, economic/
22.	*models, theoretical/
23.	*models, organizational/
24.	markov chains/
25.	monte carlo method/
26.	exp decision theory/
27.	(markov* or monte carlo).ti,ab.
28.	econom* model*.ti,ab.
29.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30.	or/21-29
31.	20 or 30
32.	3 and 31

2 **Embase search terms**

1.	exp drug hypersensitivity/
2.	((drug or medication* or medicine* or penicillin* or beta?lactam* or beta-lactam* or NSAID* or ((non?steroidal or non-steroidal) adj (anti?inflammatory or anti-inflammatory or antinflammatory)) or an?esthe*) adj2 (allerg* or hypersensitivity or sensitivity or intolerance)).ti,ab.
3.	or/1-2
4.	health economics/
5.	exp economic evaluation/
6.	exp health care cost/

7.	exp fee/
8.	budget/
9.	funding/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/4-16
18.	statistical model/
19.	exp economic aspect/
20.	18 and 19
21.	*theoretical model/
22.	*nonbiological model/
23.	stochastic model/
24.	decision theory/
25.	decision tree/
26.	monte carlo method/
27.	(markov* or monte carlo).ti,ab.
28.	econom* model*.ti,ab.
29.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30.	or/20-29
31.	17 or 30
32.	3 and 31

1

2

Appendix H: Clinical evidence tables

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H.1 Assessment

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
Agbabiaka TB, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Safety: an International Journal of Medical Toxicology and Drug Experience. 2008; 31(1):21-37[2]	Systematic review of methods for causality assessment of adverse drug reactions.	N/A	34 methods of causality assessment were found falling into 3 broad categories: expert judgement/global introspection (4 studies); algorithms (26 studies); probabilistic methods /Bayesian approaches (4 studies).	Temporal sequence; previous exposure/drug information; alternative aetiological candidates; drug level/evidence of over dose; challenge; dechallenge; rechallenge; response pattern to drug; confirmed by lab evidence; concomitant drugs; background epidemiology / clinical information; ADR characteristics / mechanism	26 algorithms compared	Probable / likely; causative; definite; possible; coincidental; exclude; unclassified/ conditional; doubtful; remote / unlikely; unassessable / unclassifiable; certain; unrelated; negative.	Narrative review provided of included algorithms. The authors conclude that confounding variables comprise the sensitivity and specificity of algorithms and thus standardised causality assessment systems to provide reliable and reproducible measures of the relationship-likelihood in suspected cases of ADR seems unfeasible.	No sources of funding were used to assist in the preparation of this review. The authors were supports by research fellowships sponsored by Dr. Willmar Schwabe Pharmaceuticals, Germany.	See description of study in the review and the criteria used to assess adverse drug reactions across various algorithms.
Arimone Y, Bidault I, Dutertre JP, Gerardin M,	Update of another French algorithm	N/A	See Begaud et al, 1985[11]	Updated criteria include a rewording of the scale for certain	N/A	Numerical scores ranging from 0–6 with	N?A	Not stated	Based on consensus only (not tested

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
Guy C, Haramburu F et al. Updating the French method for the causality assessment of adverse drug reactions. Therapie. 2013; 68(2):69-76[4]	with revision based on consensus amongst member of the Imputability Working Group			chronological and semiological criteria (leading to a more discriminating scale) and a new bibliographical and informativeness scale.		higher scores indicating a higher likelihood of adverse drug event			whether revision leads to improved classification). Even though improved it seems unlikely that it would be used in General Practice in the UK due to the number of items involved and complexity of the scoring system.
Benahmed S, Picot MC, Hillaire-Buys D, Blayac JP, Dujols P, Demoly P. Comparison of pharmacovigilance algorithms in drug hypersensitivity reactions.	Compara-tive study of 3 algorithms in the diagnosis of drug hypersensitivity	60 patients with drug allergy to beta-lactams or NSAIDS and 60 patients without allergy were	Begaud based on 7 criteria of chronology and symptoms and signs; Jones 4 general criteria with yes or no answers; Naranjo based on 10 questions with yes or no answers.	Begaud: time sequence, dechallenge, rechallenge, clinical symptoms, alternative aetiology, results of lab tests. Jones: time sequence, dechallenge, rechallenge and	Compare to gold standard allergy testing	All categories in each algorithm were used. The algorithms were compared in total.	The Jones method had better sensitivity (50%) than Begaud (8.3%) or that of Naranjo (0%). Naranjo gave better specificity (100%) than that of the Begaud method (98.3%) or that of the Jones method (53.3%). The Begaud method	Institutional grant University Hospital of Montpellier	The Jones algorithm compared favourably with the Naranjo algorithm in scoring drug hypersensitivity reactions. It is a simpler algorithm to use. The

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
European Journal of Clinical Pharmacology. 2005; 61(7):537-541[12]		compared using algorithms of Begaud, Jones and Naranjo.		alternative aetiology. Naranjo: previous reports in the literature on this reaction, time sequence, dechallenge, rechallenge, clinical symptoms, alternative aetiology, results of lab tests, reaction with placebo, dose, history of previous reaction.			gave better positive and negative predictive values (50.9% and 83.5%) than the Jones method (18.5% and 83.4%) and the Naranjo method (0% and 100%). No concordance (k=0.14) was noted between allergy diagnoses using the Jones or Naranjo methods. The Jones and Naranjo methods were perfectly concordant with one another (k=1) but the Jones method showed a substantial trend in favour of higher scores for the cases. No concordance (k=0) was noted using the Begaud method.		Begaud algorithm, although less sensitive than the Jones algorithm may be more specific with better predictive values.
Bousquet, PJ, Demoly P, Romano A,	Members of European	Used prospectively with	A standardised questionnaire was developed for use	Time to onset; Previous experience;	N/A	Probability scale: certain,	No assessment provided	European Academy of	This protocol emphasises the clinical

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
Aberer W, Bircher A, Blanca M et al. Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. Allergy. 2009; 64(2):194-203[15]	Network for Drug Allergy developed a questionnaire which provides a standardised guide for assessment of drug hypersensitivity.	3500 patients in Montpellier and disseminated to other European sites	by GPs. It takes about 5–6 minutes to complete and classifies reactions into acute (up to 24 hours) and delayed (more than 24 hours)	Alternative aetiology; response pattern (over time); lab confirmation; concomitant drugs; ADR characteristics (immediate signs and symptoms)		probable, possible, doubtful, unrelated / not assessable		Allergology and Clinical Immunology	status and includes some lab markers that are of interest in drug hypersensitivity reactions.
Busto U, Naranjo CA, Sellers EM. Comparison of two recently published algorithms for assessing the probability of adverse drug reactions. British Journal of Clinical Pharmacology. 1982;	Comparison of algorithms by Kramer(ASS) and Naranjo (APS)	63 randomly selected cases of suspected ADRs were rated independently by 2 raters.	Kramer (ASS) algorithm is a questionnaire of 57 questions; Naranjo (APS) is a questionnaire of 10 questions	ASS: 6 criteria including previous experience with drug, alternative aetiology, drug levels and evidence of overdose, timing of events, dechallenge and rechallenge. APS: pattern of response, temporal	Ratings based upon the characteristic of the ADR, the characteristic of the rater, the quality of the information and the scale used.	See criteria used	High inter-rater reliability when both methods were used: ASS scores were highly correlated (r=0.86); APS scores were similar (r=0.96). Scores obtained with APS were highly correlated with those obtained with ASS by both raters: r=0.86 and r=0.81 respectively.	Not stated	This study shows that while the ASS is somewhat more complex than APS both are equally reliable and will give similar results regarding the probability of ADRs. This represents concurrent

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
13(2):223-227[17]				sequence, dechallenge, rechallenge, alternative causes, placebo response, drug levels, dose, previous experience with the drug.			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)		validity as there is no gold standard for comparison to determine content validity.
Caimmi S, Caimmi D, Bousquet PJ, Demoly P. How can we better classify NSAID hypersensitivity reactions?--validation from a large database. International Archives of Allergy and Immunology. 2012; 159(3):306-312[20]	Development of specific NSAID allergy classification algorithm based on retrospective evaluation of data collected for 11 years	122 patients with positive allergy testing for NSAIDs	ENDA drug allergy questionnaire but new classification system developed using immediate (reaction up to 6 hours after drug exposure) and non-immediate (reaction more than 6 hours after exposure) categories	Clinical patterns of initial reactions; whether 1 or more NSAID classes were involved; the timing of reaction; underlying chronic disease; mechanism of reaction and results of SPT and challenge.	N/A	Probability scale: certain, probable, possible, doubtful, unrelated/not assessable	Authors first used the classification published by Quiralte et al and then the ENDA classification. Subsequently because some cases were left behind, a new classification system was developed.	None stated	Using the new classification system all patients could be classified; authors added 'non-immediate angioedema' that appeared between 6 and 24 hours after exposure.
Du W, Lehr VT, Lieh-Lai M, Koo W, Ward	Development of an ADR	A sample of 100 suspecte	A 13 item questionnaire was developed and	Timing; alternative aetiology;	Naranjo criterion	Definite; probable; possible;	The new algorithm is short and easy to use with validity	Gerber Foundation	Algorithm not specific to drug allergy

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
RM, Rieder MJ et al. An algorithm to detect adverse drug reactions in the neonatal intensive care unit. Journal of Clinical Pharmacology. 2013; 53(1):87-95[28]	assessment algorithm for the NICU population, real patient data from cases derived from routine clinical practice	d ADR cases were collected retrospectively from 3 NICUs	the assessments were evaluated by a group of neonatal clinical pharmacology experts and the validity and reliability were compared to the Naranjo algorithm.	overdose; dechallenge; rechallenge; lab results; response pattern; concurrent meds; background clinical information; ADR characteristics		unlikely	and reliability in the NICU population which is significantly better than the Naranjo algorithm. Validity measured by the weighted kappa statistic was 0.76% (95% CI 0.67 to 0.85) for the new algorithm and 0.31 (95% CI 0.20 to 0.41) for the Naranjo algorithm; p<0.001.		but includes all ADRs.
Gallagher RM, Kirkham JJ, Mason JR, Bird KA, Williamson PR, Nunn AJ et al. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. PloS One. 2011;	Modification of the Naranjo algorithm	40 children with suspected ADRs causing hospital admission	7 investigators assessed the 40 cases using the Naranjo scale and discrepancies were investigated and criteria modified if deemed necessary	Time sequence; previous exposure / drug information; alternative aetiology; dechallenge; rechallenge; lab results; concomitant drugs; ADR characteristics	N/A	Unlikely; probably; possible, definite	The Liverpool ADR CAT, using 40 cases from an observational study, showed causality categories of 1 unlikely, 62 possible, 92 probable and 125 definite (1, 62, 92, 125) and 'moderate' IRR (kappa 0.48), compared to Naranjo (0, 100, 172, 8)	Commissioned by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research scheme	Easy to administer and possible to use in General practice.

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
6(12):e28096[38]							with 'moderate' IRR (kappa 0.45). In a further 40 cases, the Liverpool tool (0, 66, 81, 133) showed 'good' IRR (kappa 0.6) while Naranjo (1, 90, 185, 4) remained 'moderate'.		
Gonzalez J, Guerra F, Moreno C, Miguel R, Daza JC, Sanchez Guijo P. Assessment of a self-designed protocol on patients with adverse reactions to beta-lactam antibiotics. Allergologia Et Immunopathologia. 1992; 20(5):184-189[42]	Design of a specific protocol based on clinical, causal and laboratory criteria for confirming or excluding suspicions of adverse reactions to beta-lactam antibiotics	150 patients with suspected adverse reactions to beta-lactam antibiotics	A protocol based on clinical, antigen involvement and laboratory criteria with assigned scores was applied to each patient. Patients were then classified into 3 groups according to their scores	Challenge; lab results; ADR characteristics – immediate signs and symptoms	N/A	Certain; dubious; negative	Patients in the 'dubious category' with algorithm scores of 4–8 had further skin testing or oral provocation. Of 150 patients who were analysed beta-lactam allergy was ruled out in 94 patients.	Not stated	Clinical lab test used: RAST
Kane-Gill SL, Forsberg EA,	Comparison between	Phase 1: retrospec	Kramer (ASS) uses specific rules for	ASS: 6 criteria including	APS: pattern of response,	See previous column.	Phase 1 only: Naranjo criteria		This study demonstrates

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
Verrico MM, Handler SM. Comparison of three pharmacovigilance algorithms in the ICU setting: a retrospective and prospective evaluation of ADRs. Drug Safety. 2012; 35(8):645-653[53]	Kramer, Naranjo and Jones algorithms.	tive evaluation after patient discharged from ICU/hospital of a random sample of 261 medication antidote administrations. Phase 2: relates to adverse drug reactions only using laboratory signals.	operational assessment of ADRs and originally contained 56 questions. These questions were later simplified and condensed. The Naranjo (APS) criteria is a 10 item questionnaire that categorises the probability of an ADR. The Jones algorithm contains 5 questions and is constructed so as not to allow continuation to the next question without a positive response to the prior question.	previous experience with drug, alternative aetiology, drug levels and evidence of overdose, timing of events, dechallenge and rechallenge.	temporal sequence, dechallenge, rechallenge, alternative causes, placebo response, drug levels, dose, previous experience with the drug. Jones criteria includes previous experience with drug, drug level, rechallenge, response pattern.	Levels of certainty compared including: highly probable, probable, possible, remote doubtful unlikely.	resulted in significantly more probable assessments than the Jones algorithm (p=0.009). 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. The level of certainty for each signal assessment was identical for 87.7% (229/261). 86.6% (226/261) and 93.1% (243/261) for Kramer versus Jones, Jones versus Naranjo and Naranjo versus		that agreement between algorithms is at least moderate for ADRs in the ICU. Since possible or greater likelihood rankings by causality instruments are typically the criteria of an ADR, then retro-spectively it may be acceptable to use any of the 3 causality algorithms.

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
							Kramer respectively.		
Michel DJ, Knodel LC. Comparison of three algorithms used to evaluate adverse drug reactions. American Journal of Hospital Pharmacy. 1986; 43(7):1709-1714[73]	Compar-ison of Kramer, Jones, Naranjo	Pharmac y students used the 3 algorith ms to evaluate 28 ADRs.	Kramer (ASS) uses specific rules for operational assessment of ADRs and originally contained 56 questions. These questions were later simplified and condensed. The Naranjo (APS) criteria is a 10 item questionnaire that categorises the probability of an ADR. The Jones algorithm contains 5 questions and is constructed so as not to allow continuation to the next question without a positive response to the prior question.	ASS: 6 criteria including previous experience with drug, alternative aetiology, drug levels and evidence of overdose, timing of events, dechallenge and rechallenge.	APS: pattern of response, temporal sequence, dechallenge, rechallenge, alternative causes, placebo response, drug levels, dose, previous experience with the drug. Jones criteria includes previous experience with drug, drug level, rechallenge, response pattern.	See previous column. Levels of certainty compared including: A=definite or probable; B=probable; C=possible and D=unlikely, doubtful or remote.	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.	Not stated	Overall, the agreement we observed in this study is better than would be expected if 2 raters had compared the same ADRs without using an algorithm. This study also supports Busto et al with k=0.82 when Kramer and Naranjo were compared. As Naranjo is less time consuming and is simpler to use it is recommended by these authors. More data is needed to support use

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
									of Jones.
Pere JC, Begaud B, Haramburu F, Albin H. Computerized comparison of six adverse drug reaction assessment procedures. Clinical Pharmacology and Therapeutics. 1986; 40(4):451-461[83]	Comparison of 6 algorithms for concordance. An analysis of disagreement was also done.	1134 cases	6 algorithms not specifically described	Overall percentage of agreement between pairs of methods using 7 criteria: timing;dechallenge;rechallenge;alternative aetiology; lab test; event pattern; known ADR	See previous column	A 4-class scale was used as in the majority of these methods, rated from 1 (weak) to 4 (strong causal relationship). For the 5 degree scales methods scores 0 and 1 were pooled.	The rate of agreement between any 2 methods fluctuates between 26% (Naranjo versus Emanueli) and 60% (the method of Begaud versus Emanueli) or 65% (Kramer versus Naranjo). Concordance between methods is better than with chance but never more than moderately (0.40 <kappa<0.60). Kramer versus Naranjo (k=0.51). The methods of Kramer and Naranjo present only 1 category of rank disagreement and have a higher rate of agreement (65%) and the best concordance (kappa=0.51). The	Grants from the Counseil Scientif-ique de l'Universit e de Bordeaux	Bayesian systems recommended to address discrepancies in weighting criteria.

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
							weightings of criteria were evaluated in terms of sensitivity, specificity and predictive values. Criteria are neither sensitive (0.41<Sens<0.70) nor specific (0.18<Spec<0.63) and have poor predictive values.		
Son YM, Lee JR, Roh JY. Causality assessment of cutaneous adverse drug reactions. Annals of Dermatology. 2011; 23(4):432-438[102]	Comparison of the Naranjo algorithm and a Korean algorithm to evaluate the causal association between drugs and cutaneous ADRs.	141 patients with cutaneous ADRs	The Naranjo algorithm consists of 10 questions which are scored in 4 categories; the Korean algorithm consists of 8 questions with scores in 5 categories	Time sequence; previous exposure / drug information; alternative aetiology; drug level / overdose; dechallenge; rechallenge; lab results; concomitant drugs; background epi; ADR characteristics	Previous exposure / drug information; alternative aetiology; challenge; rechallenge; response pattern to drug; lab results	Naranjo: definitely; probable; possible; and doubtful. The Korean algorithm: certain; probable/likely; possible; unlikely; and contradictory.	The 2 algorithms were significantly correlated to one another and thus reliable assessment methods to determine cutaneous ADRs: Pearsons correlation coefficient of 0.682 (p=0.0) and the measurement of inter-rater reliability by ICC was 0.67 (0.57 ≈ 0.75) which ascertains a significant	Not stated	The authors conclude that the Korean algorithm can be used more properly in ascertain risk factors earlier and reflecting prognosis than Naranjo. The Korean algorithm added proportional dos dependent responses, event

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
							correlation of the measured quantitative values of the 2 assessments.		abatement and clinical appearance on drug removal to Naranjo algorithm.
Theophile H, Andre M, Miremont-Salame G, Arimone Y, Begaud B. Comparison of three methods (an updated logistic probabilistic method, the naranjo and liverpool algorithms) for the evaluation of routine pharmacovigilance case reports using consensual expert judgement as reference. Drug Safety. 2013;	Comparison of an updated probabilistic method with the Liverpool, Naranjo algorithms with a consensual expert judgement reference standard	59 random drug event pairs sampled from spontaneous reports to the French pharmacovigilance system	Logistic probabilistic method in which 7 criteria are assessed and the answers weighted according weights obtained by a multilinear regression model.	Time to onset, dechallenge, rechallenge, search for other aetiology, risk factors for drug reaction (drug-disease or drug-drug interaction), reaction at site of application or validated laboratory test clearly in favour of the drug responsible, and previous reports or publication of similar drug-event associations	See Naranjo and Liverpool algorithms	Probability between 0 and 1. Naranjo: definitely; probable; possible; and doubtful. Liverpool: definitely; probable; possible; and unlikely.	The probability method gave results closer to the consensual expert judgment than either the Naranjo or the Liverpool algorithms.	It is stated that no sources of funding were used to assist in the preparation of the manuscript	Since the expert consensus was expressed as a probability score rather than a categorical label it was therefore likely that the statistical method would be closer to this score. Due to the scoring procedure it is unlikely to be used in general practice unless a computerised version is introduced.

Reference	Study type	Number of patients	Type of algorithm and how derived/ type of allergy information about assessors	Criteria used in the algorithm	Criteria of comparison algorithm (if applicable	Causality categories used in included algorithms	Findings	Source of funding	Comments
36(10):1033-1044[105]									
Trewin VF. The design of an algorithm for pharmacists to evaluate ADRs in the elderly. Journal of Clinical Pharmacy and Therapeutics. 1991; 16(1):45-53[106]	Development of an algorithm for the evaluation of suspected adverse drug reactions in the elderly.	N/A	Utilising data from the Pharmacheck System and consists of 6 axes. For each axis a scoring system is assigned with higher confidence in the data reflected by higher numerical values.	Alternative aetiology; dechallenge; lab results; background epi; ADR characteristics / mechanism.	N/A	Probable if total score ≥5; possible if total score is <5.	The number and types of adverse drug reactions identified in 500 admissions to a department for care of the elderly: 35 reactions in 32 classes of drugs.	Not stated	

H.2 Measuring serum tryptase after suspected anaphylaxis

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
Malinovsky et al (2008)[67]	Cross-sectional (prospective) Aim to evaluate incidence of hypersensit	31	71%	Patients with suspected hypersensitivity reaction to anaesthetics (29 general, 2 regional) at	Tryptase measurements from radioimmunoassays (RIA, Immunotech, Beckman-Coulter,	Hypersensitivity reaction diagnosed based on clinical history, mediator concentration in blood and skin	(confidence intervals calculated by analyst) With 12 microgram/ litre threshold: sens: 63.6%	(confidence intervals calculated by analyst) With 12 microgram/litre threshold: PPV: 100%	Of the ratio between T0 to T24h: sensitivity: 63% specificity: 83% PPV: 92%	Not reported	Unclear if the definition of hypersensitivity reaction in the study was anaphylaxis. Patients with just urticaria or angioedema alone were

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
	ivity reactions during anaesthesia by using histamine and tryptase measurements and allergological investigations to investigate suspected or unexplained reactions			University Hospital Nantes from May 2001 to April 2003 (hypersensitivity reaction determined if presented with cutaneous symptoms (urticaria or angioedema) isolated or in association with other clinical symptoms like bronchospasm, hypotension, or cardiovascular collapse or if circulatory inefficacy	Marseille) 30 minutes when not life threatening and between 30 and 60 minutes when life threatening Serum levels >11 nmol/l itre were considered positive; thresholds of both 12 and 25 microgram /litre were tested	tests (both prick and intradermal tests performed 4 weeks later)	(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 microgram/ litre threshold: sens: 40.9% (95% CI 20.7 to 63.6%) spec: 100% (95% CI 66.4 to 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 microgram/li tre threshold: PPV: 100% (95% CI 66.4 to 100%) NPV: 41% (95% CI 20.7 to 63.6%)	NPV: 42%		included and these patients are not likely to be considered to have anaphylaxis. 8 patients excluded from analysis because they did not undergo skin prick tests. Tryptase (and histamine) tests formed part of the reference standard leading to possible incorporation bias (which could lead to inflated agreement between index and reference tests and an inflated measure of diagnostic accuracy).

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
				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) M: 10/22 (45%), F 12/22 (55%) Patients without IgE-mediated hypersensitivity reactions:							

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
				Median age: 45 years (range: 19–78); M: 5/9 (56%), F: 4/9 (44%)							
Mertes et al (2003)[72]	Cross-sectional (retrospective) Aim to survey of allergic and non-immunity-mediated reaction during anaesthesia, description of clinical characteristics, and identification of possible factors and responsible drugs	789 with adverse reaction during anaesthesia in France between Jan 1999 and December 2000	68% (of the 259 tested for tryptase)	Of the 518 diagnosed with anaphylaxis, 70% were female and in those 15.5% had atopy, 10.7% asthma, 18.1% drug intolerance. Of the 271 with anaphylactoid reaction, 66% were female, 12.7% had atopy, 9.8% had asthma and 19.8%	UniCAP Tryptase (serum samples taken and test performed 'during adverse reaction' in 259 patients only) Serum levels ≥25 microgram/litre were considered positive	Anaphylaxis (immune-mediated reaction) diagnosed with clinical history, skin tests (prick and intradermal), or IgE assay results	(confidence intervals calculated by analyst) With 25 microgram/litre threshold: sens: 64% (95% CI 56.4 to 71.1%) spec: 89.3% (95% CI 80.6 to 95.0%)	(confidence intervals calculated by analyst) With 25 microgram/litre threshold: PPV: 92.6% (95% CI 86.3 to 96.5%) NPV: 54.3% (95% CI 45.7 to 62.8%)	Not reported	From institutional or departmental sources (not specified)	Retrospective nature of study may preclude ability to blind assessors to results of index test when performing reference standard. Also, timing of reference standard was not clear. Serum samples taken 'during reaction' but exact timing after onset of symptoms not clear. The timing of the test could have an impact on its sensitivity.

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
				drug intolerance. There was no difference in atopy, asthma and drug intolerance except in anaphylaxis group Age not reported.							Authors include only 32.8% (259/789) of patients in whom tryptase concentrations were determined at the time of the reaction. Details of other patients and reasons why tryptase tests were not performed at the time of reaction not reported; this may lead to selection bias. The accuracy of histamine was also reported.
Harboe et al, 2005[45]	Cohort study Aim to describe a patient population that developed peri-	83	A significant acute (2 hour) increase of serum tryptase accomp	Male: Female and Mean Age Female to male ratio was 3:1. Mean age was 38.2 years.	Index test Serum tryptase was measured using the Pharmacia UniCAP FEIA	Skin prick tests performed in duplicate.	Data not available	Data not available	Researchers attempted to obtain serum samples at 3 time points:	Not stated	A significant acute (2 hour) increase of serum tryptase accompanied 40 (48.2%) of the anaphylactic reactions. In 25 cases (30.1%) no

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
	anesthetic 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.		anied 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		system (Pharmacia Diagnostics) Levels were considered increased if the 2 hour serum concentration was above 24 micrograms/litre or 3 times that of the background concentration. Skin prick tests performed in duplicate.				before, within 2 hours after and on the day after the reaction.		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.

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
			serum samples were not obtained.								
Sala-Cunill et al, 2013[90]	Prospective cohort 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	102 patients with a confirmed clinical diagnosis of anaphylaxis by allergist and serum tryptase drawn during anaphylaxis.	63/102 (61.8%) showed elevated tryptase	Sex: male 39/102; female 63/102. Age: 18–65 years: 83/102; >65 years: 19/102. Etiology of anaphylaxis: Drug 51/100 (50%)	Serum tryptase using UniCAP-Tryptase fluoroimmunoassay (Phadia, now Thermo Fisher Scientific, Uppsala, Sweden) Serum tryptase concentration >11.4 microgram/litre considered high	Clinical anaphylaxis	Overall sensitivity only when due to drug: 33/51 (65%).	Data not available	Following onset of symptoms time point were: T1, 1–2 hours; T2 4–6 hours and T3, 12–24 hours.	Spanish Ministerio de Ciencia e Innovacion, Instituto de Salud Carlos III, Fondo de Investigacion Sanitaria and the Centro de Investigacion Biomedica en Rd de Enfermedades Hepaticas y Digestivas.	

Bibliographic reference	Study type and objective	Number of patients	Prevalence	Patient characteristics	Type of test	Reference standard	Sensitivity & specificity	Positive & negative predictive value	Timing	Source of funding	Additional comments
	the clinical severity of the reaction.										

Abbreviations: CI: confidence interval; IgE: immunoglobulin E; MCT: mast cell tryptase; NPV: negative predictive value; PPV: positive predictive value; RIA: radioimmunoassay; sens: sensitivity; spec: specificity; SD: standard deviation; t1/2, half-life

H.3 Measuring serum specific IgE

H.3.1 Beta-lactam antibiotics

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Blanca M, Mayorga C, Torres MJ, Reche M, Moya MC, Rodriguez JL et al. Clinical evaluation of Pharmacia CAP System RAST FEIA amoxicilloyl and benzylpeni	Study type: Case–control Data source: Patients attending at the clinical outpatient department before the skin test procedure Setting: Clinical outpatient department Country:	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	Male: Female and Mean Age Group 1: 6 women (32%) and 13 men (68%). Mean age 47.5 years. Group 2: 17 women (59%) and 12 (41%) men. Mean age 35.1 years. Group 3: 14 women (53.8%) and 12 men (46.2%). Mean age 43.8 years. Group 4: 22	Index test Pharmacia CAP System RAST FEIA amoxicilloyl c6 and benzylpenicilloyl c1. 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.	TP FP FN TN Sensitivity and specificity	Results for Groups 1–3 by hapten benzylpenicilloyl (BPO) and amoxicilloyl (AXO) TP BPO: 24 FP BPO: 1 FN BPO: 50 TN BPO: 54 Sensitivity BPO: 32% Specificity BPO: 98% TP AXO: 32	Source of funding: Pharmacia & Upjohn CAP Limitations using QUADAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described.

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
cilloyl in patients with penicillin allergy. Allergy. 2001; 56(9):862-870[14]	Spain/Italy Recruitment: Patients were considered based on skin test reactivity to penicillin	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	(88%) women and 3 (12%) men. Mean age 40.0 years. Group 5: 18 (60%) women and 12 (40%) men. Mean age 39.7 years. Mean interval between the occurrence of the reaction and sera collection for IgE: Group 1: 136 (±44) days; Group 2: 160 (±41) days; Group 3: 440 (±214) days; Group 4: Not stated Group 5: Not stated			FP AXO: 1 FN AXO: 42 TN AXO: 54 Sensitivity AXO: 43% Specificity AXO: 98% TP BPO+AXO: 37 FP BPO+AXO: 2 FN BPO+AXO: 37 TN BPO+AXO: 53 Sensitivity BPO+AXO: 50% Specificity BPO+AXO: 96%	Reference standard: None Flow and Timing: Time between event and test varied between groups with the time between event and test twice as long for Group 3. Statistical analysis with the Levene test showed that the differences were not statistically significant and thus it was assumed that the longer timing in Group 3 between event and test was acceptable.

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
		reaction to penicillin. Subjects who 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. Inclusion criteria: Subjects who developed an immediate					

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
		reaction after the administration of a penicillin derivative including anaphylaxis and urticarial. Exclusion criteria: Not described.					

1

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Fontaine C, Mayorga C, Bousquet PJ, Arnoux B, Torres MJ, Blanca M et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam	Study type: Cohort Data source: Drug Allergy and Hyper-sensitivity Database at University Hospital of Montpellier, Montpellier, France Setting: Drug Allergy Clinic, University Hospital of Montpellier,	n=45 drug allergy patients in 3 groups: Group 1 Patients with negative skin tests and positive oral provocation. Group 2 Patients with positive skin tests Group 3 Control patients with negative skin tests and good tolerance. Each group was composed of 7 urticarial, 4 anaphylaxis and 4 anaphylactic	Female: Male and Mean Age Women (66.7%) And Male (33.3%). The mean age was 38.5 years with a range of 7–67. No significant differences existed between the groups in terms of sex, atopy, time separating the clinical manifestations and allergy explorations.	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-	TP FP FN TN Sensitivity and specificity	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	Source of funding: Not stated Limitations using QUADAS 2: Patient selection: Not randomised or consecutive Index test: Blinding of assessors to reference test not described.

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
allergy. Allergy. 2007; 62(1):47-52[35]	Montpellier, France Country: France Recruitment: Subjects who developed an immediate reaction after the administratin of a beta-lactam derivative, manifesting <6 hours after the drug intake.	shock. Inclusion criteria: Subjects 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. Exclusion criteria: Not described.		lactams and drug provocation tests.			Reference standard: None Flow and Timing: Time between event and test not significantly different between groups.

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Holm A, Mosbech H. Challenge test results in patients with suspected	Study type: Cohort Data source: Patients with clinical reaction to penicillin and negative IgE	n=580 patients who had a drug challenge and 14 patients with a positive reaction. 280 patients had an original reaction within the	Male: Female and Mean Age Only the characteristics of the 14 patients with positive challenge test	Index test IgE ImmunoCAP fluorescence enzyme immunoassay system (Phadia, Uppsala, Sweden) with a cut off value of 0.35 kUA/litre. Standard analyses included those for the allergens penicilloyl G, penicilloyl V, amoxicilloyl and	Risk for reaction in patients with clinical signs and symptoms and negative IgE	A patient with a history of a mild reaction to penicillin that occurred more than 15 years previously and with no	Source of funding: None stated Limitations using QUADAS 2: Patient

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
penicillin allergy, but no specific iGE. Allergy. 2011; 3(2):118-122 [48]	were offered a challenge with penicillin V, penicillin G or both Setting: Danish drug allergy clinic Country: Denmark Recruitment: Patients were considered based clinical signs and symptoms and negative IgE. Median time between original reaction and challenge was 15 years.	previous 15 years; 275 patients had an original reaction that occurred more than 15 years earlier. Inclusion criteria: Subjects who had a history of an allergic reaction to penicillin (skin rash or angioedema) and a negative specific IgE in serum. Exclusion criteria: Not described.	were described: 7 male and 7 female patients with age range from 5–69 years; mean age 35.5 years.	ampicilloyl. Reference standard Penicillin challenge test		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%	selection: None Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing: The time interval between the original reaction and the challenge showed a significant difference between the positive and negative reactors, with a mean of 385 days for positive outcomes compared with 769 days for negative

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
							outcomes.
Kraft D, Wide L. Clinical patterns and results of radioallergosorbent test (RAST) and skin tests in penicillin allergy. British Journal of Dermatology. 1976; 94(6):593-601[57]	Study type: Cohort Data source: Patients seen either in the 2nd Department of Dermatology, University of Vienna or during consultant visits to other University or City hospitals in Vienna Setting: As above Country: Austria Recruitment: Patients who had exhibited clinical symptoms after treatment with different penicillins.	n=79 drug allergy patients in 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.	Male: Female and Mean Age M:43, F: 36 Aged from 7–75 years (average 41.05 years).	Index test RAST technique by Wide, Bennich & Johnsson. Results were considered as negative when the activity was less than mean plus 2 SD for negative controls. Reference standard Skin tests	TP FP FN TN Sensitivity and specificity Agreement: PPV NPV	The benzylpanicilloyl specific RAST showed an overall correlation of 95.1 % with PPL 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%	Source of funding: Not stated Limitations using QUADRAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing: None, Timing explicit in patient groups

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
		Inclusion criteria: Subjects who with suspected penicillin allergy. Exclusion criteria: Not described.					

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Kraft D, Roth A, Mischer P, Pichler H, Ebner H. Specific and total serum IgE measurements in the diagnosis of penicillin allergy. A long term follow-up study. Clinical Allergy. 1977; 7(1):21-28.	Study type: Cohort Data source: Patients seen either in the 2nd Department of Dermatology, University of Vienna or during consultant visits to other University or City hospitals in Vienna Setting: As above	n=204 drug allergy patients in 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	Male: Female and Mean Age Information not provided. Clinical patterns of adverse reactions to penicillin: Anaphylactic shock: 22 Urticaria: 83 Scarlatiniform or morbilliform exanthema: 51 Polymorthic exanthema: 37 Serum sickness: 4	Index test RAST by Parmacia Diagnostics. Results were expressed in Phadebas RAST classes 0, 1, 2, 3 and 4 and in this study class) was considered to be a negative test. Reference standard Skin prick tests and intradermal tests.	TP FP FN TN Sensitivity and specificity Agreement:	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	Source of funding: Austrian Research Council Limitations using QUADAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described. Reference standard: None

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
[56]	Country: Austria Recruitment: Patients who had exhibited clinical symptoms after treatment with different penicillins.	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 Iin vitroI 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. Inclusion criteria: Subjects who with suspected penicillin allergy. Exclusion criteria: Not described.				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%	Flow and Timing: Time between event and test varied between groups: 2 days for Group A and 3 weeks-5 years for Group B.

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Qiao HL, Liu JH, Yang J, Dong ZM. Relationships between skin test, specific IgE and levels of cytokines in patients with penicillin allergy. International Journal of Clinical Practice. 2005; 59(8):895-899[86]	Study type: Cohort Data source: Patients recruited from 2 Chinese hospitals Setting: Clinical outpatient department Country: China Recruitment: Patients were considered based on positive skin test and clinical symptoms after penicillin administration	n=259 penicillin allergy patients in 3 groups: Group A with historical positive skin test; Group B with immediate positive skin test; Group C with a negative skin test. Inclusion criteria: Penicillin allergy patients who developed clinical symptoms or positive skin test Exclusion criteria: Not described.	Male: Female and Mean Age Group A: 110 cases with mean age 19.03±2.83 years; 57 males and 53 females. Group B: 122 cases with mean age 40.24±18.02; 51 males and 71 females. Group C: 27 cases with a negative skin test.	Index test Radioallergosorbent test (RAST) using discs prepared for benzylpenicilloyl, phenoxomethylpenicilloyl, ampicilloyl, amoxicilloyl, benzylpenicillanyl, phenoxomethylpenicillanyl, ampicillanyl and amoxicillanyl ploPatienylysine. Reference standard Intradermal tests in all subjects with benzylpenicillin G at a concentratin of 500 U/ml.	TP FP FN TN Sensitivity and specificity	Group B: 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	Source of funding: Engineering Project for Medical Innovative Scholars of Henan Province and the Science Foundation for Distinguished Young Scholars of Henan Province. Limitations using QUADAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing:

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
						specific IgE were 45.7, 57.1, 85.2 and 100% respectively.	Time between event and test not well described.

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Sanz ML, Garcia BE, Prieto I, Tabar A, Oehling A. Specific IgE determination in the diagnosis of beta-lactam allergy. Journal of Investigational Allergology and Clinical Immunology. 1996; 6(2):89-93 [93]	Study type: Cohort Data source: Sera from patients who had been diagnosed with adverse reaction to beta-lactams Setting: Not stated Country: Spain Recruitment: Not described	n=149 patients with a very suggestive history of drug allergy Inclusion criteria: Subjects who had clinical history of drug allergy Exclusion criteria: Not described.	Male: Female and Mean Age Not described	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	TP FP FN TN Sensitivity and specificity	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%	Source of funding: Not stated Limitations using QUADAS 2: Patient selection: Not well described Index test: Blinding of assessors to reference test not described. Reference standard: Method of skin testing not described. Flow and

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
							Timing: Time between event and test not stated.

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Sanz ML, Gamboa PM, De Weck AL. Clinical evaluation of in vitro tests in diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy and Clinical Immunology International. 2002; 14(5):185-193 [92]	Study type: Cohort Data source: Patients presenting with immediate symptoms after beta-lactam Setting: University Clinic of Navarra, Pamplona or of Basurto Hospital, Bilbao Country: Spain Recruitment: Patients who visited the allergy clinic	n=79 patients having presented immediate symptoms after beta-lactam administration 30 control patients presenting with non-allergic drug reaction and who had negative skin tests to beta-lactams and tolerated systemic beta-lactams. Inclusion criteria: History of anaphylaxis or urticarial-angioedema immediately following administration of	Male: Female and Mean Age 32 men and 47 women; average age 53.6±16.2 years. Characteristics of controls: 13 men and 17 women; average age 52.5±14.9 years.	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.	TP FP FN TN Sensitivity and specificity	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-	Source of funding: Not stated Limitations using QUADAS 2: Patient selection: None Index test: Diagnostic tests were performed by different persons and none of them knew the results of the other tests. Reference standard: None

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
	with immediate symptoms after taking a beta-lactam	beta-lactams and at least 1 positive skin test with some of the beta-lactam derived reagents used Exclusion criteria: Not described.				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 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	Flow and Timing: Time between event and test varied and in 17 cases exceeded the recommended 6 month maximum.

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
						for 2 subgroups Group 2a: Skin test positive to AX/AMPI (ampicillin), BP not done AND 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%	

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Silva R, Cruz L,	Study type: Cohort	n=67 consecutive patients	Male: Female and Mean Age	Index test Pharmacia CAP System (Phadia)	TP FP	Only 33 patients had full range of	Source of funding: None

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Botelho C, Cadinha S, Castro E, Rodrigues J et al. Work up of patients with history of beta-lactam hypersensitivity. Allergologia Et Immunopathologia. 2009; 37(4):193-197[98]	Data source: Patients with suspected beta-lactam hypersensitivity referred to Drug Allergy division of Hospital S. Joano Setting: Specialist Allergy clinic Country: Portugal Recruitment: Referred for suspected drug allergy to beta-lactams.	Inclusion criteria: Patients referred to Drug Allergy Division with history of beta-lactam hypersensitivity Exclusion criteria: Not described.	54 female; 13 male. Mean age 36.6±19.3 years (4–78 years)	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.	FN TN Sensitivity and specificity PPV NPV	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%	stated Limitations using QUADAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing: Not stated

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Vega JM, Blanca M, Garcia JJ, Carmona	Study type: Cohort	n=54 cases of immediate AX allergy with good tolerance of PG.	Male: Female and Mean Age	Index test RAST – radiolabeled substance uptake test using discs treated with	TP FP FN	All 54 patients were either skin test or challenge test positive to	Source of funding: Fondo Investigacion Sanitaria grant

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
MJ, Miranda A, Perez-Estrada M et al. Immediate allergic reactions to amoxicillin. Allergy. 1994; 49(5):317-322 [109]	Data source: Patients with history of an immediate allergic reaction to amoxicillin (AX) and good tolerance of penicillin G (PG). Setting: Carlos Haya Hospital Country: Spain Recruitment: Selection of patients from those diagnosed as allergic to beta-lactam antibiotics	23 cases had challenge tests with AX. Inclusion criteria: Subjects who developed an immediate reaction after the administration of amoxicillin and had good tolerance of PG. Exclusion criteria: Patients with positive skin test or positive challenge to BP; previous sensitisation to PG	Mean age 34 years (range 14–70); 28 were female and 26 male.	PG and AX. Reference standard Skin prick test, intradermal or drug provocation tests.	TN Sensitivity and specificity PPV NPV Pre-test probability	AX. TP 22 FP 0 FN 33 TN 0 Sensitivity of RAST for AX: 40% Specificity of RAST for AX: Unable to calculate	Limitations using QUADAS 2: Patient selection: Not described. Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing: Time between event and test not described.

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Vultaggio A, Matucci A, Virgili G, Rossi O, Fili	Study type: Consecutive cohort	n=34 patients Inclusion criteria:	Male: Female and Age Age range (year): 18–67;	Index test CAP system FEIA (Phadia, Uppsala, Sweden) for specific IgE antibodies. Serum in this sample was analysed	TP FP FN	Diagnostic performance of new and old CAP system for	Source of funding: None

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
L, Parronchi P et al. Influence of total serum IgE levels on the in vitro detection of beta-lactams-specific IgE antibodies. Clinical and Experimental Allergy. 2009; 39(6):838-844 [112]	Data source: Patients with history of suspected immediate ADR to beta-lactams in the past year and a positive skin test. Setting: Immunoallergy Department, University of Florence Country: Italy Recruitment: Consecutive patients referred to Immunoallergy Department	Subjects with suspected beta-lactam allergy and positive skin test. Exclusion criteria: Patients with negative skin tests or those who refused skin testing	Male: 11; female: 23.	for IgE towards the hapten c1 (penicilloyl G), c2 (penicilloyl V), c5 (ampicilloyl) and c6 (amoxicilloyl). Serum samples were considered positive when 1 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 or intradermal test.	TN Sensitivity and specificity PPV NPV Pre-test probability	beta-lactam allergy: Sensitivity (95% CI): New test 0.85 (0.69–0.95) Old test 0.44 (0.27–0.62) Specificity (95% CI): New test: 0.54 (0.44–0.63) Old test 0.80 (0.72–0.87)	Limitations using QUADAS 2: Patient selection: None Index test: Blinding of assessors to reference test not described. Reference standard: Oral challenge not used Flow and Timing: Time between event and testing up to 215 days.

H.3.2 Neuromuscular blocking agents

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Fisher MM, Baldo BA. Immunoas	Study type: Cohort	n=347 patients who experienced anaphylaxis in 4	Male: Female and Mean Age	Index test Radio immune assay for morphine	TP	Group 1 results only:	Source of funding: Drug company

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
says in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. Anaesthesia and Intensive Care. 2000; 28(2):167-170 [34]	Data source: Patients defined as experiencing anaphylaxis on the basis of a positive serum mast cell tryptase and positive skin test to 1 or more NMBAs. Setting: Not described Country: Australia Recruitment: Not described	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 4 Patients who had suspected anaphylaxis, serum mast cell tryptase levels were not elevated and no skin testing	Not reported.	and radio immune assay for specific IgE Reference standard Intradermal skin testing	FP FN TN Sensitivity and specificity	Positive skin test and positive specific IgE RIA: 47/69 (68%) Positive skin test and positive Morphine RIA: 67/69 (97%).	producing Morphine RIA Limitations: Patient selection: Selection method not well described Index test: Blinding of assessors to reference test not described. Conduct of test not well described. Reference standard: None Flow and Timing: Unclear when serum for RIA testing taken.

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
		was performed Inclusion criteria: Subjects who experienced anaphylaxis on the basis of a positive serum mast cell tryptase result and a positive skin test to 1 or more NMBAs. Exclusion criteria: Not described.					

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Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Laroche D, Chollet-Martin S, Leturgie P, Malzac L, Vergnaud MC, Neukirch C et al. Evaluation of a new routine diagnostic test for	Study type: Cohort Data source: Patients who reacted during anaesthesia in 2001–2007 Setting: University hospitals at Caen and Paris	n=114 patients who reacted during anaesthesia. Group A: 57 reactors were selected on the basis of immediate reactions after NMBA injection, increased concentrations of histamine or tryptase, and a	Group A: Mean age (±SD): 51 (±15) years. Age range 19–82 years. Male: 20, Female: 37. Group B: Mean age (±SD): 48 (±17) years. Age range 10–82 years. Male: 21,	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.	TP FP FN TN Sensitivity and specificity	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%	Source of funding: Research grant from PhadiaAB, Uppsala, Sweden Limitations using QUADAS 2: Patient selection: Retrospective

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
immunoglobulin e sensitization to neuromuscular blocking agents. Anesthesiology. 2011; 114(1):91-97 [61]	Country: France Recruitment: Patients were selected from a cohort who reacted during anaesthesia, had blood samples taken during the reaction and with their informed consent, had skin tests at least 4 weeks after the reaction.	positive skin test to the administered NMBA Group B: 57 reactors with negative skin test to NMBAs during the same period. Inclusion criteria: Patients who reacted during anaesthesia. Exclusion criteria: Not described.	Female: 36.				Index test: Blinding of assessors to reference test not described. Reference standard: None; appropriate for NMBAs Flow and Timing: Time between event and test at least 4 weeks.

H.3.3 Chlorhexidine

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
Garvey LH, Kroigaard M, Poulsen LK, Skov PS, Mosbech H, Venemalm	Study type: Case control Data source: Patients investigated at the Danish	n=22 patients with strong suspicion of allergy to chlorhexidine because of repeated or delayed reactions and results of	Male: Female and Mean Age 17 males /5 females; Median age in in STP group 64 years; median	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:	TP FP FN TN Sensitivity and specificity	Sensitivity: 91.7% Specificity: 100% PPV: 100% NPV: 91%	Source of funding: None stated Limitations using QUADAS 2:

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison (Index test and reference standard)	Outcome measures	Effect sizes	Comments
L et al. IgE-mediated allergy to chlorhexidine. Journal of Allergy and Clinical Immunology. 2007; 120(2):409-415[40]	Anaesthesia Allergy Centre Setting: Allergy centre Country: Denmark Recruitment: Patients were investigated because of suspected allergic reactions in connection with anaesthesia and surgery.	initial skin testing. Inclusion criteria: As above. Patients were divided into 2 groups – skin test positive (STP, n=12) and skin test negative STN, (n=10). Exclusion criteria: Not described.	age in STN group 49 years.	Skin prick tests in all subjects. Intradermal tests if prick test was negative.			Patient selection: Not consecutive or random Index test: Blinding of assessors to reference test not described. Reference standard: None Flow and Timing: Not explicitly stated

H.4 Documenting and sharing information with other healthcare professionals

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Abramson EL, Barron Y, Quaresimo J, Kaushal R. Electronic prescribing	Prospective non-randomised before	Number of prescriptions at baseline n=2432 and n=2079 at 1 year	Prescriptions were prospectively collected in 21 ambulatory care providers in New York State	Paper prescriptions at baseline and e-prescriptions 1 year later (6 providers)	Paper prescriptions at baseline and paper prescriptions 1 year later (15	1 year	Prescribing errors (excluding illegibility errors and rule violations)	1 year group comparison - e-prescripti	Agency for Health care Research and	Adverse drug reactions were defined but unclear how

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
within an electronic health record reduces ambulatory prescribing errors. Joint Commission Journal on Quality and Patient Safety. 2011; 37(10):470-478[1]	–after design with concurrent controls	Physician review and classification: 2 physicians independently reviewed all suspected near misses and Adverse drug reactions in which ADRs were assessed using the Naranjo algorithm (therefore covering drug allergy)			providers)			ons/total: 86/536 Paper: 592/1543	Quality	or in what percentage errors resulted in these reactions
							Rule violations – errors unlikely to cause harm (such as failure to write 'po' for oral medication)	1 year group comparison - e-prescriptions/total: 31/536 Paper: 872/1543		
							Near missed (prescribing errors with potential but not resulting in harm – for example prescribing for a patient with a known allergy but medication being intercepted).	1 year group comparison - e-prescriptions/total: 86/536 Paper: 592/1543		
							Alert Advanced errors (prescribing errors preventable	1 year group comparison - e-		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of fundin g	Comments
							with advanced decision support)	prescripti ons/total : 14/536 Paper: 334/1543		
							Alert Basic (prescribing errors preventable with basic clinical decision support)	1 year group comparis on - e-prescripti ons/total : 70/536 Paper: 160/1543		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N et al. The impact of computerized physician order entry on	Prosp ective time series with 4 period s Count ry: USA	All patients admitted to 3 medical units for 7 10- week periods in 4 different years. Baseline (before introduction	Participants were all patients admitted to a study floor during a study period Baseline: Duration days 51, Patient days 1704, Admissions 379, Medication orders	Physician order entry (POE) checks each order for completeness and ensures that certain parameters come from standard lists. Suggested doses and frequencies are offered for	At baseline orders were written on paper without automated decision support	No follow-up (separat e time periods)	Documented allergy errors Number of occurrence of errors followed by rate per 1000 patient days in parentheses	Baseli ne: 10 (5.9); Period 1: 1 (0.4); Period 2: 1 (0.6); Period 3: 0	Risk Managem ent Foundatio n	Only a very limited number of event errors were recorded even at baseline, no adjustments for other confounding

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
medication error prevention. Journal of the American Medical Informatics Association. 1999; 6(4):313-321[8]		of computerised physician order entry – POE) Period 1 (first period after introduction of new system) n=10,070 medication orders; Period 2: n=15,025; Period 3: n=13,139; Period 4: n=14,352	10070, Medication orders/patient-days 5.91, Medication orders / admission 26.6 Period 1: Duration days 68, Patient days 2619, Admissions 492, Medication orders 15025, Medication orders/patient-days 5.74, Medication orders / admission 30.5 Period 2: Duration days 49, Patient days 1784, Admissions 471, Medication orders 13139, Medication orders/patient-days 7.36, Medication orders / admission 27.9 Period 3: Duration days 51, Patient days 1878, Admissions 475,	medication orders. Entered orders are screened for problems such as drug allergies and drug-drug interactions and the system presents these problems to the physician immediately when appropriate. During Period 2 and 3 the system was refined with improved drug allergy checking in Period 2 and improved potassium ordering and drug-drug interaction checking in Period 3						variables was attempted.

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Medication orders 14352, Medication orders/patient-days 7.64, Medication orders / admission 30.2							

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. JAMA. 1998; 280(15):1311-1316[7]	Phase I: Before-and-after study Phase II: Randomised comparison Note: this present review only analyses data from Phase I, and between Phase I and Phase II. The main intervention in Phase II entails a	Hospital units: 6 adult non-obstetrical units at a tertiary care hospital Number of admissions: 2491 Number of patient-days: 12,218	Hospital units: 1 medical intensive care unit 1 surgical intensive care unit 2 medical general care units 2 surgical general care units Patients: Mean age of patients (±SD): 52.5 (±18.6) years	Physician Computer Order Entry (POE) system	N/A	Phase I ran for 6 months	Mean rate of non-intercepted serious medication errors [Defined as those that either resulted in or had potential to result in an adverse drug events (ADEs) and were not intercepted before reaching the	Before: 10.7 events/1000 patient-days After: 4.86 events/1000 patient-days MD: −5.84 events/1000 patient-days p=0.01	The Risk Management Foundation, Boston, Massachusetts, and the American Society of Health-System Pharmacists Foundation, Methesda, Maryland, USA.	This present review only analyses data from Phase I, and between Phase I and Phase II. The main intervention in Phase II entails a number of potential confounders

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	number of potential confounders		M: 49.1%, F: 50.9% White ethnicity: 75.6%				patient.]			
	Objective To evaluate the efficacy of 2 interventions for preventing non-intercepted serious medication errors						Number of medication errors, specifically, number of known allergies	Before: 8 (0.65) After: 7 events (0.29/1000 patient-days) MD: −0.36 events/1000 patient-days p=0.009		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Benkhaial A, Kaltschmidt J, Weisshaar E, Diepgen TL, Haefeli WE. Prescribing errors in patients	Retrospective data analysis? Objective i) To allocate different drugs and drug groups to ICD-	200	A random sample of adult in-patients at a university hospital M: 95 (47.5%), F: 105 (52.5%) Age range: 19	(Pseudo-intervention) Using ICD-10 codes for drug allergy documentation	(Pseudo-comparator) Using manually written chart for drug allergy documentation	Data were obtained in 2007	General outcomes: 12/56 patients (21%) with documented drug allergies were prescribed 23	N/A	Unrestricted educational grant from Libya	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
with documented drug allergies: comparison of ICD-10 coding and written patient notes. Pharmacy World and Science. 2009; 31(4):464-472[13]	10 codes as guidance for allergy alerts to systemically administered drugs. ii) To evaluate the value of using ICD-10 codes as guidance for allergy alerts to systemically administered drugs in an electronic drug prescribing system iii) To analyse handwritten allergy information in a representative random sample of in-patients' charts to assess the quality of electronic coding and the		to 96 (mean: 59±17) Number of patients with drug allergy: 56/200 (28%) Allergy info documentation format: ICD-10 code only: 5 patients (8.9%) Written in chart only: 38 patients (67.9%) Both: 13 patients (23.2%)				times an allergy-inducing drug either as the same culprit drug (52%) or as a cross-reacting compound (46%). 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). Proportion of patients with ICD-10 having medication error: 20% Proportion of patients with			

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	relationship between prescribing errors and location of allergy documentation in the chart.						manual documentation having medication error: 21.6%			

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Brown S, Black K, Mrochek S, Wood A, Bess T, Cobb J et al. RADARx: Recognizing, Assessing, and Documenting Adverse Rx events. Proceedings. 2000;101-105[16]	Indirect comparative study Objective Not clearly stated.	N/A The total number of events entered into the CPOE system between July 1999 and September 1999 were 1,643.	Veterans Administration Medical Centre (VAMC) Nashville and Veterans Integrated Service Network (VISN) 9 developed the intervention, 'RADARx' (Recognizing, Assessing, and Documenting Adverse Rx [prescription]	RADARx is a computer software that integrates computerised ADE screening, probability assessment, documentation and reporting. It evaluates the existing information system's patient data every 4	No RADARx (just the Veterans Health Administration's existing information system)	3 months	Number of ADEs Number of potential ADEs Number of ADEs found by RADARx Number of potential ADEs found by RADARx Number of ADEs found by traditional methods	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	Not reported	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%

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			events).	hours for occurrences of medications or lab values that indicate a possible ADE. RADARx produces FDA MedWatch-compatible documentation by guiding the user through a structured interview and by retrieving data from the current information system in use.				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		true positive rate. The different categories of counts as shown on the left are not defined clearly in the article.

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Colpaert K, Claus B, Somers A, Vandewoude K, Robays H, Decruyenaere J. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. Critical Care. 2006; 10(1):R21[23]	Non-randomised comparative study Objective To investigate if the introduction of a computerised intensive care unit (ICU) reduces the incidence and severity of medication prescription errors (MPEs).	Intervention: 1 computerised unit (C-U) with 8 beds Control: 2 paper-based units (PB-U) with a total of 14 beds Total number of prescription: 2,510 of which: C-U: 1,286 PB-U: 1,224	Participants had been admitted to a surgical ICU in a tertiary care university hospital. Mean age C-U: 61.5 years PB-U: 54 years p=0.021 Drug prescriptions C-U: 17 PB-U: 15 p=0.386 Length of stay C-U: 2 days PB-U: 5 days p=0.016	CPOE / Intensive care information system (ICIS), which is a computerised system specifically designed for intensive care units	Paper-based medication prescription order system	10 months post-implementation of ICIS in the intervention group	Incidence of different levels of medication prescription errors (MPEs)	Total medication prescribing errors (MPE) 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 Total ADEs Computerised unit: 2/1286 (0.2%) Paper-based units: 12/1224 (1.0%) p<0.001	Not reported	Rates of MPEs in a 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. Serious MPEs are defined as non-intercepted potential adverse drug events (ADEs) or ADEs. The allergy status of the patient was shown by

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								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.		means of a differentially 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.

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Coombes ID, Stowasser	Prospective before-and-after	Pre-implementation: 730 patients,	A collaborative of doctors, nurses and	Standardised revised medication	N/A	Data were collected 4 months	All prescribing errors	Pre-implementation:	Queensland Health Safe	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
DA, Reid C, Mitchell CA. Impact of a standard medication chart on prescribing errors: a before-and-after audit. Quality and Safety in Health Care. 2009; 18(6):478-485[25]	observational audit	9772 orders Post-implementation: 751 patients, 10,352 orders 5 out of the 7 hospital sites took part in the before-and-after observational audit	pharmacists from 7 hospitals in south Brisbane was established to address statewide and local medication safety issues in 2002. A standardised medication chart including revised ADR documentation alerts and warfarin management was agreed as an initial priority.	chart		before the intervention in 2002 and 6 months after the intervention in 2003.		2300/9772 (23.5%) Post-implementation: 1935/10352 (18.7%)	Medication Practice Program	
							Number of patients with ≥1 errors	Pre-implementation: 591/730 (81.0%) Post-implementation: 587/751 (78.2%)		
	Objective 1. To develop and implement a standard medication chart, for recording prescribing and administration of medication in public hospitals in Queensland. 2. To assess the chart's impact on the						Prescribing errors per patient (median; range)	Pre-implementation: 2; 0–20 Post-implementation: 2; 0–17 p=0.182 ARR=2.9% RRR=3.5%		
							Percentage of errors per order per patient	Pre-implementation: 20.0% Post-implementation: 15.8%		

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	frequency and type of prescribing errors, adverse drug reaction (ADR) documentation and safety of warfarin prescribing. 3. To use the chart to facilitate safe medication management training.							p=0.03 ARR=4.2% RRR=21.0%		
							Number of patients with ADRs and the incidence of ADRs	Pre-implementation: 185 patients (25.3%), 302 ADRs Post-implementation: 197 patients (26.2%), 311 ADRs		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Eneh O, Fahy S. Audit of documentation of allergies in a psychiatric inpatient unit. Irish Journal of Psychological Medicine.	Before after study (audit and re-audit)	Initial audit: medication charts from 109 (44% female) inpatients; Re-audit: medication charts from 105 inpatients	Participants were inpatients from 6 psychiatric wards (2 acute inpatients and 4 long stay units)	A formal assessment pro forma with a clearly designated allergy section.	Before and after implementation	Not applicable	Level of compliance with documentation of allergy – Medication charts	Before 25% After 58.1%	Not stated	The intervention did not only include the pro forma, but also 'renewed awareness of the importance of
							Level of compliance with documentation	Before 12% After 19.1%		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
2011; 28(4):213-216[30]		(49% female)					of allergy – current case notes			documentation of allergy status was created amongst doctors and nurses. Details of the intervention were only vaguely described.
							Level of compliance with documentation of allergy – original admission notes	Before 65% After 80.9%		
							Compliance in the acute unit	Documentation compliance in the acute unit shows only modest improvement		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Evans RS, Pestotnik SL, Classen DC, Horn SD, Bass	Prospective study	n=79,919 hospitalised patients during a 44	Patients in a 520-bed private tertiary care hospital and a	A computerised system to monitor the occurrences of ADEs in	Time – series: first year of implementation followed by	See comparison	Type B Adverse drug events defined as:	Year 1: 13; 20; 23 Year 2: 0;	Supported in part by a grant	Special in-service education concerning

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
SB, Burke JP. Preventing adverse drug events in hospitalized patients. Annals of Pharmacotherapy. 1994; 28(4):523-527[33]		months period	major teaching center in Utah, USA	hospitalised patients. The system is part of the computerised hospital information system known as Health Evaluation through Logical Processing (HELP). The computer system identifies clinical manifestations, such as rush, change in respiratory rate, heart rate, hearing, or mental state, seizure, anaphylaxis, diarrhoea, or fever that are entered into the computer through routine nurse bedside charting or by nurses and pharmacists who explicitly report possible ADEs. In addition the computer	1 year and 2 year results		allergic or idiosyncratic in nature. These were further subdivided into – known allergies (where a previous allergic reaction had been identified); inappropriate administration (rapid administration); and first time use	1; 7 Year 3: 0; 2; 16	from the agency for Health Care Policy and Research	the common clinical manifestations of ADEs and instructions on how to use the computer to report possible ADEs were provided for all nurses and pharmacists at the onset of the project and periodically thereafter.
							Overrides	1% (it was stated 'the physician changed the drug order 99% of the time when they were notified)		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
				monitors all laboratory test results, drug concentrations, and pharmacy orders for signals of possible ADEs. The knowledge base in the system uses computerised logic to evaluate information in the computerised medical record and identifies patients who may have experienced a drug reaction as defined by WHO.						

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Evans RS, Classen DC, Pestotnik SL, Clemmer TP, Weaver LK, Burke JP. A decision support tool for	Before-and-after study Objective To describe the development and initial	Pre-implementation: 626 patients admitted to the study ward Post-	Patients admitted to the Shock / Trauma / Respiratory Intensive Care Unit (STRICU)	CPOE / Clinical decision support (CDS) tool integrated into the HELP system	Before and after implementing the CDS tool	1 year pre-implementation period followed by 7 months post-implementation	Incidence of ADEs due to antibiotics (out of the number of patients receiving antibiotics)	Pre-implementation: 15/403 (3.7%) Post-implementation: 3/233	Not reported	*LDS HELP: LDS Hospital (Salt Lake City, Utah, USA) Health Evaluation through Logical

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
antibiotic therapy. Proceedings / the Annual Symposium on Computer Application [Sic] in Medical Care Symposium on Computer Applications in Medical Care. 1995;651-655[31]	evaluation of a decision support tool (DST) to improve the use of and reduce the cost of antibiotics	implementation: 336 patients admitted to the study ward						(1.3%)		Programming **BICS: Brigham Integrated Computing System 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.

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, Jr. et al. A computer-assisted management program for antibiotics and other antiinfective agents. New England Journal of Medicine. 1998; 338(4):232-238[32]	Prospective cohort study	n=1681 Pre-intervention: n=1136 During intervention: n=545 (of those: Computer regimen followed n=203 Computer regimen overridden n=195)	Pre-intervention period: Mean age During the intervention period: Mean age: 48 years M: 59%, F: 41% Number of patients receiving anti-infective agent: 398 (73%)	Computerised anti-infectives management programme	Comparison arms: i) Pre-intervention [P] ii) During intervention plus computer regimen always followed [DC] iii) During intervention plus computer regimen sometimes overridden (these participants did not always receive the computer-suggested anti-infective regimen) [DO]	Throughout the 1-year intervention period (July 1994 to June 1995) the participants were evaluated on a daily basis and their care was managed with use of the programme.	The outcomes here have been selected for their relevance to this present review. Unadjusted outcome: Number of drug allergy alerts* Number of adverse events caused by anti-infective agents* *The numbers for the 2 intervention period groups are not available separately. Mortality	1) Number p=146 DC+DO: 35* 2) Number p=28 DC+DO: 4* 3) Mean (±SD) p=172 (±22) DC: 36 (±18) DO: 52 (±27)	Intermountain Health Care	
	Objective	Inclusion criteria					Adjusted outcomes	4) Mean (95% CI)		

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	To study the use of the computerised anti-infectives management programme in an intensive care unit and to evaluate its effect on the quality of patient care.	All patients admitted to the study site (respiratory intensive care unit in an acute care hospital) between July 1992 and June 1995					(adjusted for age, sex, Computer Severity Index score, medical service and mortality): Number of different anti-infective agents ordered Number of days of excess anti-infective dosage Total length of stay in hospital (days)	p=2.0 (1.9 to 2.1) DC: 1.5 (1.3 to 1.7) DO: 2.7 (2.5 to 3.0) p<0.001 5) Mean (95% CI) p=5.4 (4.5 to 6.4) DC: 1.4 (0 to 2.7) DO: 3.6 (2.0 to 5.1) p<0.001 6) Mean (95% CI) p=12.9 (11.5 to 14.4) DC: 10.0 (7.7 to 12.3) DO: 16.7		

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								(14.2 to 19.1) p<0.001		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Hackl WO, Ammenwerth E, Marcilly R, Chazard E, Luyckx M, Leurs P et al. Clinical evaluation of the ADE scorecards as a decision support tool for adverse drug event analysis and medication safety management. British Journal of Clinical Pharmacology. 2013; 76(S1):78-90[44]	Controlled interrupted time series analysis, qualitative interviews and standardised survey Objective To investigate the usage and acceptance of ADE scorecards by healthcare professionals (HCPs) and their impact on rates of	5 medical units of a hospital (3 intervention units versus 2 control units)	Intervention unit 1: Cardiology & Gastroenterology Intervention unit 2: Internal Medicine & Infectious Diseases Intervention unit 3: Acute Geriatric Care Control unit 1: Surgery Control unit 2: Pulmonology	ADE scorecards (Use of a tool called 'ADE scorecards' was intended to increase 'team' ADE awareness by making automatically derived information on the number and on the possible causes of recent possible ADE cases	No ADE scorecards	Apr 2009–Jun 2010: pre-implementation (15 months) Jul 2010–Sep 2012: post-implementation (15 months)	Primary outcome: Monthly rates of possible ADEs Secondary outcomes: Usage and acceptance of ADE scorecards by HCPs	Rate of detected ADE cases (per 1000 inpatient stays) @ 15 months pre-implementation @ 15 months post-implementation Intervention Dep. A Pre-implementation: 218 Post-implementation: 172	European Community Seventh Framework Programme – the Patient Safety through Intelligent Procedures in medications (PSIP) project	All 13 of the interviewed healthcare professionals (HCPs) considered the ADE scorecards to be useful to support decision-making and they expressed their intention to use the ADE scorecards as part of an ADE prevention approach. In the survey

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	possible adverse drug events (ADEs).			available to the entire team as opposed to a single HCP using a CPOE system.)				Intervention Dep. B Pre-implementation: 289 Post-implementation: 287 Intervention Dep. C Pre-implementation: 305 Post-implementation: 247 Control Dep. D Pre-implementation: 78 Post-implementation: 85 Control Dep. E Pre-implementation: 21 Post-implementation: 24		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 HCPs were convinced that ADE scorecards could contribute to increased medication safety.

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								The regression analysis comparing the pre and post periods in each department and comparing intervention and control departments, showed no significant changes in ADE rates after the introduction of the ADE scorecards.		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Harris MF, Giles A, O'Toole BI. Communication across the divide. A trial	Randomised controlled trial Objective	155 GPs	The GPs had practices in an ethnically diverse population with areas	A structured pro forma for GP-ED communication, based on a minimum data	Usual referral procedures	The data obtained were based on referrals which	Number of referral letters that GPs sent out Number of intervention	Intervention: n=307 Control: n=225 Intervention: n=34 (11%)	The Commonwealth Department of Health and Aged	In the study, it is stated that the control group

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
of structured communication between general practice and emergency departments. Australian Family Physician. 2002; 31(2):197-200[46]	To evaluate the impact of structured form letters for general practitioner (GP) to emergency department (ED) communication.		of low socioeconomic status in Sydney.	set developed from previous audits conducted by the Department of General Practice in South West Sydney and discussions with ED staff and GPs in the area. On the reverse side of this form was a brief set of information which the ED could fax back to the GP with information on the outcomes of the referral.		took place over 5 months from June to October 1998 inclusive.	pro formas used	Control: n=4 (2%)	Care General Practice Evaluation Program	GPs did not receive the intervention pro forma, however, the outcome suggests that some control GPs (2%) used the intervention pro forma.
							Number of times 'allergies' was included in the referral letters	Intervention: n=55 (18%) Control: n=27 (12%)		
							Proportion of GPs who reported to have received faxed discharge letters from ED	10% (not ideal)		

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Reference	Study type	Number of participants	Participant characteristic	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Hippern LD, Halapy H. Assessing penicillin allergies with a structured	Prospective patient interview and retrospective review of existing records	60	Patients at a day surgery unit All with	Structured penicillin allergy assessment form	Medical chart	Participants were enrolled between January and	The medical chart documented penicillin allergy for at	N/A	Not reported	

Reference	Study type	Number of participants	Participant characteristic	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
assessment form. Canadian Journal of Hospital Pharmacy. 2000; 53(3):184-192[47]	Objective To compare the current unstructured method of recording penicillin allergy at a hospital with use of a structured penicillin allergy assessment form.		suspected allergy to penicillin Age range: 19 to 86 (mean: 59±17) M: 26 (43%), F: 34 (57%)	(completed in an interview given by a pharmacist)		May 1998.	least 58 out of the 60 participants (97%). However, the interview using the structured assessment form revealed that: 18 patients (30%) had a probable true allergy 32 patients (53%) had a possible true allergy 8 patients (13%) had a side effect or intolerance 2 patients (3%) were unlikely to have allergy			

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Reference	Study type	Number of participants	Participant characteristic	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Hsieh TC, Kuperman GJ,	Retrospective chart review	1,608	M: 95 (47.5%	Overriding of	Not overriding	Data were of	A total of 6,182 of 7,761 alerts (80%)	N/A	Grant from the	

Reference	Study type	Number of participants	Participant characteristic	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Jaggi T, Hojnowski-Diaz P, Fiskio J, Williams DH et al. Characteristics and consequences of drug allergy alert overrides in a computerized physician order entry system. Journal of the American Medical Informatics Association. 2004; 11(6):482-491[49]	Objective To determine characteristics of drug allergy alert overrides, assess how often they lead to preventable adverse drug events, and suggest methods for improving the allergy-alerting system.		F: 105 (52.5%) Age range: 19 to 96 (mean: 59±17) Number of patients with drug allergy: 56/200 (28%)	computerised alerts	computerised alerts	patients admitted to the hospital during a 3-month period between August and October 2002.	were overridden in 1,150 patients Only 120 out of 1,150 (10%) overridden allergy alerts were triggered by an exact match between the ordered drug and the listed drugs. Thus, 90% of overriden alerts were triggered by non-exact drug/allergy matches, in which the drug and allergy had structural similarities or were in the same family but were not identical. Override reasons given by physicians: Aware / will monitor: 55% Patient does not have this allergy / tolerates: 33%		National Library of Medicine and a student research grant from Harvard Medical School	

Reference	Study type	Number of participants	Participant characteristic	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							Patient taking drug already: 10% Other: 3% Rates of adverse drug events owing to overridden allergy alerts: Significant: 53% Serious: 47% Life-threatening: 0% Fatal: 0% (Total number of adverse drug events: 19)			

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Hunteman L, Ward L, Read D, Jolly M, Heckman M. Analysis of allergy alerts within a computerized prescriber-	Retrospective analysis of medication orders	Total orders n=49,887 (1 month of inpatient orders of which 643 triggered allergy alert in a 314-bed	Majority of patients were white (88%) and female (65%) with a median age of 66 years (range 24–94 years.	CPOE system	Not applicable	Not applicable	Number of allergy alerts	643 /49887 (1.3%) for a total of 289 patients		[including risk of bias assessments, per outcome as necessary]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
order-entry system. American Journal of Health-System Pharmacy. 2009; 66(4):373-377[51]		academic hospital in Florida, USA)						with an average of 2 orders triggering alerts per patient.		
							Override rate	625/643 (97%)		
							Reasons for overrides: Benefits outweigh risks, Patient previously tolerated, Therapeutically appropriate, Free text explanation	 29% 49% 24% 8%		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Kuperman GJ,	Retros	2 hospitals,	Not described	Computerised	2 other CPOEs	7 days	Frequency	80%	Grant	Many issues

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Gandhi TK, Bates DW. Effective drug-allergy checking: methodological and operational issues. Journal of Biomedical Informatics. 2003; 36(1-2):70-79[59]	pectiv e review	Massachuse tts, USA		physician order entry system at the Brigham and Women's Hospital: Reactions that the patient experiences when exposed to allergens are not required; reasons to override drug allergy alerts are required but not coded; Cross sensitivity checking is present in the system; and reverse allergy checking is present in the system	but data not described		of overrides reported.		from the National Library of Medicine	remain unclear, 3 systems are described but data was only reported for 1. Overrides reported but not reported of how many overall orders. Reactions not reported. Features of the system not linked to the overrides.
							1 week's worth of overrides	1043		
							Reason's for overrides	Has tolerated in past: 349 (33%); 'Aware': 278 (27%); Will monitor or follow: 159 (15%); Not really allergic: 68 (7%); Other: 189 (18%)		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Leung AA, Schiff G,	Before-and-after study	n=1590 patients at	Inclusion criteria:	Each hospital	Comparison 1	Pre-impleme	Primary outcome:	Comparison 1	The Rx Foundation	The target population

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Keohane C, Amato M, Simon SR, Cadet B et al. Impact of vendor computerized physician order entry on patients with renal impairment in community hospitals. Journal of Hospital Medicine. 2013; 8(10):545-552[62]	Objective To determine whether computerised physician order entry (CPOE) systems with clinical decision support capabilities reduce the frequency of renally related adverse drug events (ADEs) in hospitals.	5 community hospitals Pre-implementation: n=775 Post-implementation: n=815	Patients with renal failure ≥18 years Exposed to potentially nephrotoxic or renally cleared medications Admitted to any of the 5 participating hospitals between January 2005 and September 2010 Baseline characteristics (of those enrolled during post-implementation): Mean age: 72.2 M: 57%, F: 43% Caucasian: 87.4%	independently selected a vendor CPOE system 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,	Before and after implementing CPOE Comparison 2 Between different levels of CDS capability (between the study sites)	ntation: 20 months Post-implementation: 23 months	Rate of preventable ADEs Secondary outcomes: Rates of potential ADEs Overall ADEs	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	and Commonwealth Fund	was limited to renal failure patients and the outcomes were related to nephrotoxicity or accumulation of a renally excreted medication. Therefore, the cases recorded and data analysed in this study are not generalisable to all hospital inpatients and outpatients, and they are clearly not limited to allergies. Definitions

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
			Hispanic: 3.3% African American: 6.0% Other or unknown: 3.3%	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)				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 Comparison 2 Number of potential		provided by the study: Adverse drug event (ADE): any drug-related injury Preventable ADE: an ADE due to an error at the time of order entry Non-preventable ADE: any drug-related injury in which there was no error at the time of order entry. Medication error: an error anywhere in the process of

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								ADEs increased significantly after implementation of CPOE at all levels of CDS capability ($p<0.01$) Number of ADEs (per 100 admissions) Basic CPOE only: Pre-implementation: 5.6 Post-implementation: 9.5 p=0.08 CPOE plus lab display: Pre-implementation: 10.3 Post-implementation: 8.9		prescribing, transcribing, dispensing, administering, or monitoring a drug, but with no potential for harm or injury. Potential ADE: an error with the potential to cause harm, but not resulting in injury, either because it was intercepted or because of chance.

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								p=0.55 CPOE plus lab display plus drug-dosing check: Pre-implementation: 12.4 Post-implementation: 4.2 p=0.02		

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Reference	Study type	Number of patients	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Mahoney CD, Berard-Collins CM, Coleman R, Amaral JF, Cotter CM.	Before-and-after study	2 teaching hospitals associated with a medical school	N/A	Computerised physician order entry (CPOE) system	N/A	12 months pre-implementation and 12 months post-implementation	Number of prescribing errors after implementation of a clinical decision-support system (CDSS): Pre-implementation: 833	N/A	Not reported	

Reference	Study type	Number of patients	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Effects of an integrated clinical information system on medication safety in a multi-hospital setting. American Journal of Health-System Pharmacy. 2007; 64(18):1969-1977[66]							Post-implementation: 109 OR=0.14 (95% CI 0.11 to 0.17) p<0.001			

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Marco AP, Buchman D, Lancz C. Influence of form structure on the anesthesia preoperative	Randomised retrospective chart review	217 charts (from 112 older forms and 105 newer forms) were reviewed.	The charts were of patients undergoing surgical procedures in the operating rooms at an academic health centre.	The revised form of a new anaesthesiology preoperative evaluation form. Background: - Before 1999, a basic evaluation	The pre-1999 evaluation form	N/A	Number of times allergy component was present in the forms	Older form: 111/112 (99%) Newer form: 102/105 (97%)	Not reported	
	Objective To examine the						Test of the difference in proportions of completed documentatio	z=1.08 SE of differ-ence=0.02 (95% CI −0.03		

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
evaluation. Journal of Clinical Anesthesia. 2003; 15(6):411-417[68]	configuration of a standardised preoperative anaesthesia form to determine its effect on documentation of representative elements of the pre-anaesthesia assessment.			form was used. - In April 1999, a new form was developed, which had prompts for many medical history items and specific elements needed for billing, compliance and general assessment. - In August 1999, this was revised and reprinted using new software for consistency in appearance with other hospital forms which were being developed.			n between older and newer forms	to 0.02) That is, the difference in proportion of completed documentation on allergy is not statistically significant.		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Mead GE, Cunnington	Prospective	300 medical admissions –	208 were from a GP in the patient's	Assessment of quality as well as	203 used headed note	Not applicab	Overall quality Pro forma:			[including risk of bias

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
AL, Faulkner S, Russell KJ, Ford MJ. Can general practitioner referral letters for acute medical admissions be improved? Health Bulletin. 1999; 57(4):257-261[70]	review of GP admission letters	no letters were received from 9 admissions, (n=291)	own practice, 79 from GP cooperative and 4 from deputising service. 267 were handwritten 10 were typed and 14 combined both.	content of admission letter Content was assessed as satisfactory, unsatisfactory or absent and legibility (easy, difficult and illegible) Content categories were demographic details current history, past history, social history, drugs, allergies and provisional diagnosis. 82 letters used pro formas	paper	le	Excellent Good Adequate Inadequate Headed note paper: Excellent Good Adequate Inadequate	7% 43% 38% 12% 12% 42% 38% 8% 'There was no difference in the overall quality nor were there any significant differences in recording of individual		assessments, per outcome as necessary]

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								items of content'		
							Quality of content for allergies: Satisfactory Unsatisfactory Absent	 16% 1% 83%		
							Legibility of information on allergies: Satisfactory Unsatisfactory Absent	 70% 4% 26%		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Menendez MD, Alonso J, Rancano I, Corte JJ, Herranz V, Vazquez F. Impact of computerized physician order entry on	Before-and-after study Objective To describe the epidemiology and	n=1553 patients, who were associated with 1887 medication errors	Acute geriatric inpatients at a hospital	CPOE / Clinical electronic record (CER) It has 3 main screens: 1) Prescription screen 2) Drug	Pre-CPOE period / Hand-writing system	6 years (3 years pre-implementation and 3 years post-implementation)	Number and type of medication errors	Rate of errors Pre-implementation: 356 errors per 7001 discharges (5.1%) Post-implementation: 1197	Not reported	The study participants are limited to the acute geriatric population of a single hospital in Spain.

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
medication errors. Revista De Calidad Asistencial. 2012; 27(6):334-340[71]	severity of medication errors detected in an acute geriatric hospital, and the impact of the electronic clinical record on reducing errors.			substance in the pharmacy hospital repository and the rest of the drugs 3) Standard procedures and a free narrative text				errors per 11,347 discharges (10.5%) RR=2.07 (99% CI 1.79 to 2.40) 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)		The CPOE system was from Germany (Selene, Siemens). *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).

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Mullett CJ, Evans RS, Christenson JC, Dean JM.	Before-and-after study	Pre-implementation: n=809 patients	Children and young people admitted to a PICU in a	CPOE / Anti-infective decision support tool	Before and after implementing the system	6 months pre-implementation	Impact of introducing the DST was	Impact on drug allergy alerts PICU: No	The University of Utah, Intermoun	This paediatric DST was based on a

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Development and impact of a computerized pediatric antiinfective decision support program. Pediatrics. 2001; 108(4):E75[75]	Objective To evaluate the impact of an anti-infective decision support tool in a paediatric intensive care unit (PICU).	Post-implementation: n=949 patients	primary children's medical centre	(DST) for a paediatric unit		followed by 6 months post-implementation	compared between a paediatric intensive care unit (PICU) and adult shock-trauma intensive care unit (STICU) from a previous study.	change STICU: Large reduction Impact on ADEs attributable to anti-infectives PICU: No change STICU: Large reduction	tain Health Care Corporation, and the National Library of Medicin	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.

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Neubert A,	Before-and-	n=773	i) n=474 male	ADR	Intensive	6	Sensitivit	Department	German	Pre-

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Dormann H, Prokosch HU, Burkle T, Rascher W, Sojer R et al. E-pharmacovigilance: development and implementation of a computable knowledge base to identify adverse drug reactions. British Journal of Clinical Pharmacology. 2013; 76 Suppl 1:69-77[80]	after study Objective To convert knowledge of adverse drug events (ADRs) available from plaintext drug information into computable knowledge formats using standardised medical classifications. Additionally, to implement the application into clinical routine and compare the signals generated within intensive chart review to determine the potential sensitivity and specificity of	patients (which led to 913 hospital admissions)	patients admitted to a 29-bed gastro-enterological ward over a 6-month period Number of admissions: 474 Average length of hospital stay: 9.3 days Mean age: 54.5 years ii) n=496 paediatric patients admitted to a 22-bed paediatric isolation ward over a 6-month period Number of admissions: 439 Average length of hospital stay: 5.2 days Mean age: 6.1 years	knowledge base (ADR-KB) that incorporates patient data from hospital information systems (HIS)	chart review	months	y and specificity of ADR-KB in detecting ADRs	of internal medicine Pre-implementation sensitivity: 91% Post-implementation sensitivity: 88.2% Pre-implementation specificity: 23% Post-implementation specificity: 32.2% Department of paediatrics Pre-implementation sensitivity: 90.3%	Israeli Foundation (GIF), Bayerisches Staatsministerium 'Bayern aktiv', Marohn Stiftung and Doerenkamp Professorship for Innovations in Animal and Consumer Protection	implementation: Computerised monitoring system purely on laboratory data with no link to the prescribed medicines Post-implementation: Use of ADR-KB with HIS combined Sensitivity: The number of ADR positive patients alerted by at 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

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	the system and thus the impact of this approach on signal quality.							Post-implementation sensitivity: 82.3% Pre-implementation specificity: 19.6% Post-implementation specificity: 53.1%		relation to the total number of non-ADR patients

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Ortega A, Aguinagalde A, Lacasa C, Aquerreta I, Fernandez-Benitez M, Fernandez LM. Efficacy of an adverse drug reaction	Retrospective data analysis followed by a before-and-after analysis Objective	Total of 222 ADRs were reported.	Every ADR reported through the ADR-RS-IHIS between April 2004 and April 2007 was evaluated.	ADR reporting tool ('ADR-RS-IHIS')	After the end of study, outcomes from Phase I and Phase II were compared.	Phase I: 29 months (Apr 2004–Aug 2006) → Evaluated the efficacy of the ADR-RS-IHIS	Summary of the 5 improvement measures proposed Nurses could report ADRs in the same way as physicians to avoid losing information. Yellow Cards could be filled out directly from the ADR-RS-IHIS to decrease the number	N/A	Not reported	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of participants</th><th>Participant characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Effect sizes</th><th>Source of funding</th><th>Comments</th></tr>
<tr><td>electronic reporting system integrated into a hospital information system. Annals of Pharmacotherapy. 2008; 42(10):1491-1496[81]</td><td>To analyse the efficacy of an adverse drug reaction (ADR) reporting tool integrated into the hospital information system in increasing ADR reporting to the national drug surveillance system.</td><td></td><td></td><td></td><td></td><td>Interim period (Apr 2006) → Interim analysis which led to proposal of 5 improvement measures.

Phase II: 8 months (Sep 2006–Apr 2007) → Evaluated the impact of the 5 improvement measures proposed.</td><td>of Yellow Cards which were not sent as well as to decrease the time involved.
The allergy department could see all of the ADRs that were suspected allergies.
Additional information to be filled in by the pharmacist when evaluating ADRs was incorporated, so that the data could be automatically and quickly obtained.
Training sessions were proposed regarding the importance of ADR reporting, how to distinguish an allergic reaction, and reaction management.

Summary of the impact of the 5 improvement measures:
<table>
<tr><td></td><td>Phase I</td><td>Phase II</td></tr>
<tr><td>Number of reports</td><td>165</td><td>57</td></tr>
<tr><td>Documented on patient chart</td><td>82</td><td>49</td></tr>
<tr><td>Suspected allergy</td><td>90</td><td>24</td></tr>
<tr><td>Studied</td><td>15</td><td>5</td></tr>
</table></td><td></td><td></td><td></td></tr>
</table>

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures			Effect sizes	Source of funding	Comments
							allergy					
							Yellow cards sent	27	13			
							Yellow cards necessary	44	19			
							ADR reports per month	5.69	7.1			
							Yellow cards per month	0.91	1.62			
							'Yellow Card' When a pharmacist receives the notification of an ADR report via an alert in the computer system, he/she could then evaluate it and decide whether it should be reported to the national drug surveillance system via a Yellow Card.					

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Porter SC, Manzi SF, Volpe D, Stack AM. Getting the	Observational (qualit	256 parent-child dyads were observed at triage in	Convenience sample of parent-child dyads arriving for care at a single tertiary	Not applicable	Not applicable	Not applicable	Bracelets	Of 28 cases assessed as having	Grants from the agency for Healthcar	The focus of the paper is not on documentation /

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
data right: information accuracy in pediatric emergency medicine. Quality and Safety in Health Care. 2006; 15(4):296-301[84]	y improvement project)	paediatric emergency medicine (Boston, USA)	care paediatric ED					an allergy 16 (57.1 %) were noted to have a bracelet. For 5 of those the information on the bracelet was incorrect (2 not matching the assessment and 3 blank)	e Research and Quality and the Department of medicine Children's Hospital Boston	communication strategies, but rather on the accuracy of triage. It is purely observational and it is therefore difficult to derive clear conclusions from the results since no interventions were carried out.
							Medication orders	111 patients had at		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								least 1 medication ordered during ED care. Of those with a true medication allergy 5/111 (4.5%) cases were noted to have a medication order sheet where the allergy history was docume		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
								d as negative or was missing.		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Sard BE, Walsh KE, Doros G, Hannon M, Moschetti W, Bauchner H. Retrospective evaluation of a computerized physician order entry adaptation to prevent prescribing errors in a pediatric emergency department. Pediatrics. 2008;	Retrospective before and after comparison	420 patient visits before and after implementation (randomly selected) Setting: Paediatric emergency department (USA)	Before quicklist: Visits n=420; orders n=326; Visits ≥1 order n=180; urgency level: High n=102 Low n=318; According to age group: 0–2 n=64 2–9 n=112 9–14 n=49 14–21 n=195 Attending physician n=62 Resident n=264 After quicklist: Visits n=420; orders n=398;	CPOE with an additional quicklist containing the 75 most commonly prescribed medications in the hospital. The patients weight and allergies are listed on the same screen. The system contains drug allergy and interaction alerts.	CPOE without quicklist, that is, medications chosen from a master list of drugs including medication that do not necessarily appear the department's formulary and may not be available. Once selected there are blank fields for doses, route and frequency.	Not applicable	Total errors Errors per 100 visits Errors per 100 orders	Before ;After: 101;55 24;13 31;14	Alpert Children of the city endowment, Robert Wood Johnson Physician Faculty Scholor Award and National Institute of Child Health and Human Development	Very little information is provided about how the system without the quicklist deals with drug allergies. The aim of the study is to reduce overall prescribing errors rather than drug allergy errors.
							Number of errors per 100 orders (allergy)	2;0		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
122(4):782-787[94]			Visits ≥1 order n=192; urgency level: High n=105 Low n=315; According to age group: 0–2: n=75 2–9: n=117 9–14: n=49 14–21: n=179 Attending physician: n=89 Resident: n=309							

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes				Source of funding	Comments
Schadow G. Structured product labeling improves detection of drug-intolerance issues. Journal of the American	Non-randomised comparative study Objective	The dataset included 1,005,187 intolerance records for 84,030 patients, covering a time range	M: 1/3, F: 2/3 Born between 1917 and 2008	[SPL] Health Level 7 / US Food and Drug Administration Structured Product Labelling (SPL) drug knowledge representati	[Gopher] RI Gopher CPOE system (the existing CPOE system)	N/A	Number of issues detected (only allergy figures are shown here) Overall result	Objects Orders Allergens Supplies Allergens Although <70% of terms were mapped to SPL, it detected 4 times as many	Total 2,734,787 1,623 3,682,962 1,623	SPL 45,129 (1.7%) 375 (23%) 13,749 (0.4%) 112 (7%)	Gopher 10,239 (0.4%) 270 (23%) 3,337 (0.1%) 94 (6%)	Agency for Healthcare Research and Quality (AHRQ) US Food and Drug Administr	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Medical Informatics Association. 2009; 16(2):211-219[95]	To compare the performance of the drug-intolerance issues detection by the Regenstrief Institute (RI) Gopher computerised physician order entry (CPOE) system with a new method using structured product labelling (SPL) and its public knowledge sources.	between 1977 and 2008.		on standard and its associated terminiology sources for drug-intolerance (allergy) decision support in CPOE				drug intolerance issues on twice as many patients.	ation (FDA)	

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Simmonds M, Petterson J. Anaesthetists' records of pre-operative assessment. British Journal of Clinical Governance. 2000; 5(1):22-27[99]	Retrospective chart review followed by a before-and-after study Objective To audit the quality of preoperative assessment recorded by anaesthetist, then use the results to improve the level of recording of preoperative assessment by designing and introducing a customised, formatted assessment sheet for voluntary use	First audit: records of 195 patients Second audit: records of 227 patients	Setting: Hospital Inclusion criteria: Patients undergoing elective or urgent general, gynaecological, vascular, orthopaedic, trauma, oral, maxillofacial, ear, nose and throat, and throat surgery Exclusion criteria: - Children under 16 years old - Day case patients Patients undergoing specialist pain relief procedures - Obstetric	A new preoperative assessment sheet	N/A	First audit: Nov 1998–Mar 1999 Second audit: Aug 1999–Oct 1999	Frequency of recording of allergy by anaesthetists Mean number of core aspects* recorded *2 authors agreed that 12 'core aspects' of a patient's preoperative assessment should be recorded by the anaesthetist for every patient in their care. 12 core asepcts Past medical history Previous anaesthetic history Drug history Allergies Smoking	First audit: 79/195 (40.5%) Second audit: 75/227 (33.0%) MD= −7.5% First audit: 3.22 (Mode: 1) Second audit: 3.26 (Mode: 2)	Not recorded	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	by anaesthetists.		surgery - Procedures performed under local anaesthesia without anaesthetic support				Airway assessment Dentition Chest examination Heart sounds Gastro-oesophageal reflux Blood pressure Family history			

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Soller RW, Shaheen C, Yen J, Rose J, Lightwood J. Erratum to Improvement of the Drug Allergy Alert for Nonprescription NSAIDs (Drug Information Journal, 46, 3 (336-343), 10.1177/0092861512440951). Drug Information Journal. 2012; 46(5):627[100,100,101,101]	Non-randomised comparative study Objective To compare revised and existing ibuprofen over-the-counter (OTC) allergy alerts for usability, readability,	Respondents to the online descriptive survey: n=170	M: 46.0%, F: 54.0 Mean age: 45 White: 81.1% Asian: 5.6% Hispanic: 5.2% African American: 2.6% Other: 5.6% College graduates: 68.1%	Revised OTC ibuprofen allergy alert Revision made based on: - literature review - survey results - focus group pre-testing Revision incorporated:	Previous version of OTC ibuprofen allergy alert	N/A	1) Overall preference (naïve consumers) 2) Overall preference (DIA survivors) 3) Usefulness for 1st time use (naïve consumers	1) Existing alert: 22% Revised alert: 78% 2) Existing alert: 0% Revised alert: 100%	The authors received no financial support for the research, authorship, or publication of this article.	

Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
	and overall preferences in consumers naïve to drug allergies and drug-induced allergy survivors.			- Steven-Johnson syndrome - time to onset and DIA risk before medication - mouth sores, specific facial regions and severe skin damage - trouble breathing in place of asthma			) 4) Usefulness for 1st time use (DIA survivors)	3) Existing alert: 24% Revised alert: 76% 4) Existing alert: 9% Revised alert: 91% p<0.001 for all 4		

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Soto CM, Kleinman KP, Simon SR. Quality and correlates of medical record	Retrospective review of records	Electronic records from 834 patients receiving care from 167 physicians	Physicians were divided into internists and paediatricians therefore patient characteristics varied widely.	The electronic system (EpicCare) has designated, coded fields	Not applicable	Not applicable	Completion of drug allergy documentation in electronic record	Internists 61.1% Paediatricians 50.4%	Research fellowship from the Harvard Medical School Office of	The study was not designed to address quality of allergy documentati

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
documentation in the ambulatorycare setting. BMC Health Services Research. 2002; 2:1-7[103]									Enrichment Programs	on directly. The main aim was to determine whether there were any physician characteristics that led to better quality documentation. Therefore results are only indirect.

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Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R et al. A randomized trial of the effectiveness of on-	Cluster randomised trial	n=14 physicians in the on-demand group (with 1550 patients) n=14 physicians in	Physicians were neligible for inclusion if they were general practitioners or family physicians in full-time practice in Montreal	MOXXI electronic prescribing and integrated drug management system using a personal digital assistant that was connected by wireless networks to a central server.	MOXXI electronic prescribing and integrated drug management system as descried in the previous	6 months	Percentage of physicians changing levels of alerts Percentage changing to most	50% computer triggered 21% on demand 35.7% computer triggered 14.3% on demand	Canadian Institutes of Health Research	Method of randomisation and allocation concealment not described, blinded only to outcome but not

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
demand versus computer-triggered drug decision support in primary care. Journal of the American Medical Informatics Association. 2008; 15(4):430-438[104]		the computer triggered group (with 1899 patients)	All patients in the practice who consented to participate had at least 1 prescription written by the study physician and visited the study physician during the follow-up period.	It provides customisable levels of alerts for all major types of prescribing problems: excess dose, drug allergy, drug-drug, drug-disease, drug-age contraindications and therapeutic duplication. Sensitivity of alerts can be customised according to 3 levels: 1: definite and serious adverse effects; 2: likely adverse effects; 3: possible adverse effects. For overrides reasons can be chosen from a dropdown menu. Computer triggered decision support functions in the background and displays alerts at 2 points in the	column. On-Demand decision support The on-demand system could be activated, by clicking on drug review in the system's menu, at any time during the prescribing process. Apart from this all other functions were the same as in the previous column		serious alerts (level 1) only			intervention, baseline difference in system usage Drug allergy category not separately analysed
							Total number of prescription problems Percentage not seen due to alert setting Percentage not seen due to not using the MOXXI	On demand: n=4445 56.5% 29.6% Computer triggered: n=6505 67.7% 22.1%		
							Total problems seen; Percentage acted on	On demand: 41 75.6%; Computer triggered: 668 12.1%		
							Reasons for ignoring	On demand: Benefit greater than risk 10%, Interaction already known		

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
				drug management process (according to the level selected by the physician. First when chart is opened. Drug alerts highlighted by an exclamation mark and colour coded by severity using a traffic light system. The second checking stage is at time of refill or new prescription. For each alert ignored physician was required to give a reason.				90%; Computer triggered: Benefits greater than risk 27.1%, drug disease information incorrect 16.5%, interaction already known 19.2%, need to consult with prescribing physician 6.1%, No time at this visit 0.9%, not clinically important 29.5%, patient resistant to change 0.7%		

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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures		Effect sizes	Source of funding	Comments
							Type of prescription	Frequency of intercepte			
Varkey P, Aponte P, Swanton C, Fischer D,	Retrospective survey Objective	Study sample: n=4,527 prescriptio	Prescriptions were ordered for patients	Computerised physician order entry (CPOE)	Other types of prescription	Analysis was carried out on			N/A	Not reported	

<table>
<tr><th>Reference</th><th>Study type</th><th>Number of participants</th><th>Participant characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow-up</th><th>Outcome measures</th><th>Effect sizes</th><th>Source of funding</th><th>Comments</th></tr>
<tr>
<td>Johnson SF, Brennan MD. The effect of computerized physician-order entry on outpatient prescription errors. Managed Care Interface. 2007; 20(3):53-57[108]</td>
<td>To evaluate the effect of computerised physician order entry (CPOE) system on pharmacist-intercepted prescription errors in the outpatient setting and to determine the type and prevalence of intercepted errors in handwritten and computerised prescriptions.</td>
<td>ns ordered during the study period</td>
<td>seen at the ambulatory (adult and paediatric) clinics at Mayo Clinic, Rochester, Minnesota. Information obtained included prescription ID number, type of prescription (computerised / written / verbal / pre-printed), date of prescription, any type of alteration made on the prescription by the pharmacist.</td>
<td>system</td>
<td>s</td>
<td>medications which were ordered through the outpatient pharmacies between 1996 and 2002.</td>
<td>
<table>
<tr><td></td><td>d prescription errors</td></tr>
<tr><td>Handwritten prescriptions</td><td>7.4%</td></tr>
<tr><td>Computerised prescriptions</td><td>4.9%</td></tr>
<tr><td>Pre-pritned prescriptions</td><td>1.7%</td></tr>
</table>
p=0.0048 between handwritten and computerised prescriptions
<table>
<tr><td>Year</td><td>Frequency of intercepted prescription errors</td></tr>
<tr><td>1996</td><td>6.21%</td></tr>
<tr><td>2002</td><td>3.97%</td></tr>
</table>
<table>
<tr><td>Type of prescription</td><td>Number of intercepted prescription errors*</td></tr>
<tr><td>Handwritten</td><td>Approx. 13</td></tr>
<tr><td>Computerised</td><td>Approx. 3</td></tr>
</table>
*The actual figures are not given in the article, thus, they
</td>
<td></td><td></td><td></td>
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Reference	Study type	Number of participants	Participant characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
							have been extrapolated from their bar chart.			

1

Reference	Study type	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect sizes	Source of funding	Comments
Zenk KE, Randall RJ, Fukumitsu CJ. Notation of allergies and body weight on patient profiles. Drug Intelligence and Clinical Pharmacy. 1984; 18(7-8):625-626[114]	Prospective study with 3 18-day time periods (baseline, intervention and post-intervention)	Baseline n=87 admissions; intervention: n=93 admissions; post intervention (without intervention): n=93 admissions Setting: Peadiatric hospital (USA)	Not described	An allergy and weight card in which physicians were asked to fill in the child's allergies and body weight in spaces provided (that is, a structured form).	Forms without designated space for allergies or weight of the child	Not applicable	Allergy information completion rate	Pre: 33.3% During: 74% Post: 47.3%	Not stated	Despite additional training, completion rate went down when the intervention was removed making a stronger case for the effect being related to the structured card.

2

H.5 Providing information and support to patients

Study	Arnott 2012[5]
Aim	To inform the management of communication about ADRs in children and to identify any unmet psychological, information and communication needs described by parents.

Study	Arnott 2012[5]	
Population	Parents of 44 children with suspected adverse drug reactions; Edinburgh	
Methods	Semi-structured interviews	
Analysis	Grounded theory methods applied to fit with focus on informing practice. Respondent validation and multi-disciplinary investigator triangulation used to ensure quality and clinical relevance.	
Themes with findings	Little explanation of the risks of medicines at the time they were prescribed.	Clinicians tended not to explain the risks of medicines when the medicines were prescribed.
		Parents reported difficulties with written information about medicine and potential ADRs.
		An exception was parents of children with cancer.
	Critical about ADR management and communication	Parents describe being overwhelmed with fear about their child's symptoms and complained that communication about their child's allergy did not meet their need for information about child's management or for reassurance.
		Communication was contradictory and poorly coordinated and timed.
	Implications of poor communication about suspected ADRs	Lack of information prevented parents from being involved in decisions about their child's care
		Fear of repetition of the ADR and reluctance to give medications in the future
	How communication should be handled	Dialogue with clinicians should help parents understand what had happened to their child, including what ADR meant for their child's future healthcare and what steps would be taken to help prevent further ADRs and to ensure that.
Limitations	• Uncertain if needs expressed are those of the child or parent. • Not all eligible families participated; Yellow card group self-selected. • Time lapse between event and study.	

1

Study	Butt 2011[18]
Aim	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.
Population	14 adult survivors of SJS and TEN; 2 hospitals in UK
Methods	Retrospective qualitative study using detailed semi structured interviews

Study	Butt 2011[18]	
Analysis	Interview transcripts were analysed in 5 steps and independently analysed by 3 researchers	
Themes with findings	Interpretation of why the ADR occurred	Survivors held different beliefs regarding the cause of the ADR. The majority believed that the reaction was avoidable (that is, due to ignoring existing allergies or administering too high a dose)
	Support and communication during the event	Most felt well supported
		Majority relied on internet for more information
		Some contacted patient support groups for sufferers of SJS and TEN
Limitations	• Unable to use purposive sampling and cohort may not be representative • View of survivors of life threatening ADRs may differ from views of those of other serious ADRs and extrapolation may not be appropriate	

1

Study	Butt 2012[19]	
Aim	To interpret the reasons for individuals with serious ADRs posting on the internet and 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.	
Population	Adult survivors of SJS and TEN; 208 internet descriptions	
Methods	First person written narratives by patients, relatives or friends. 139 descriptions were posted by patients, 69 by relatives and 1 was jointly submitted by patient and relative. Of those posted by relatives, 30 were posted by mothers.	
Analysis	NVivo used for analysis which allowed mapping of themes from the current study onto themes identified from previous analysis of interviews with survivors, suing a top-down thematic approach.	
Themes with findings	Motives for submitting an internet description	• Desire to share experience and provide support for others • Asking for advice from others • Requesting funds to treat complications
	Fears and concerns	• Fear of recurrence and subsequent avoidance of medication • Fears connected with future fertility and pregnancy • Fear that ADR was linked with development of other illnesses
Limitations	• Reporting bias with elderly patients using Internet less frequently • Only most common search engines used in this study	

1

Study	Franic 2000[36]	
Aim	There were 6 objectives over all, 1 of which was: 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)	
Population	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	
Methods	Cross sectional field study using survey instruments	
Analysis	Questionnaires were analysed using SPSS 7.5 and either percentages of means and standard deviations were reported.	
Themes with findings	Presentation of risk	• Numerical interpretations are preferred to describe risk for ADRs
Limitations	• Study population all female and well educated (over 90% held college degrees)	

2

Study	Hughes 2002[50]	
Aim	To investigate the knowledge of patients with regard to the side effects of over the counter medicines and the source of this information	
Population	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.	
Methods	Ethnographic interviews and focus groups in Welsh School of Pharmacy, Cardiff University, UK	
Analysis	Interviews were tape recorded and the transcripts analysed through a process of de-contextualisation and re-contextualisation. Focus groups discussions were tape-recorded and transcripts analysed with the aid of NUD*IST computer software.	
Themes with findings	Knowledge of side effects	• Timing of reaction • Side effect listed in patient information leaflet • Symptoms was unusual
	Information sources	• Healthcare professionals • Friends and family • Books • Media • Internet

Study	Hughes 2002[50]	
		• Patient information leaflet: writing too small; info relating to children's doses confusing; long lists of side effects may cause patients to wrongly attribute symptoms to their medication.
Limitations	• Qualitative study in which subjectivity may cause bias	

1

Study	Krska 2011A[58]	
Aim	The aim was to determine how reporters to the Yellow Card Scheme identify adverse drug reactions.	
Population	1362 questionnaires, 27 telephone interviews and data from 230 Yellow Card reports all collected in the UK	
Methods	A qualitative analysis from 3 sources was carried out: responses to 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.	
Analysis	Data from the questionnaire responses were categorised by 2 researchers independently then discrepancies discussed and agreement reached. Interview data was recorded, transcribed verbatim and analysed using constant comparison. Data from the content of Yellow Card reports was red and coded by more than 1 researcher and where there was not full agreement over the codes or the interpretation of the data these were discussed and reviewed.	
Themes with findings	Information explaining causal association	• Read about side effects on internet • Health professional informed them • Patient information leaflet
	Reasons to suspect drug allergy	• Timing of reaction • Never had the drug before
Limitations	• Qualitative study in which subjectivity may cause bias	

2

Study	Laaksonen 2002[60]
Aim	The aim was to explore the characteristics of medical patients, their information requirements, relationships with their perceptions about prescribed medicines and co-existent adverse drug effects
Population	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).

Study	Laaksonen 2002[60]	
Methods	Semi structured questions explored patients' perceptions of the adverse effects of prescribed drugs.	
Analysis	Patient data were analysed using descriptive and inferential statistics to explore relationships between the patient characteristics, their scores to the EID scale and the Naranjo scores. Patient responses to the semi-structured questions were transcribed, coded and imported into QSR NUD*IST software.	
Themes with findings	Patient's desire for information	• Patients who had experienced ADR more likely to desire information about their medications.
Limitations	• Qualitative study in which subjectivity may cause bias	

1

Study	Lorimer 2012[65]
Aim	To explore patients' experiences of severe ADR and their views on reporting their ADRs to the Yellow Card scheme
Population	Patients with severe ADR admitted to a hospital for severe drug reactions 7 out of 15 had allergic reactions; including • angioedema – enalapril (1), enoxaparin (1), clarithromycin (1) • Stevens–Johnsons syndrome to sulfasalazine (1) • severe rash to penicillin (1) • severe urticaria to 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).
Methods	Semi structured interview template was 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.

Study	Lorimer 2012[65]	
Analysis	After transcription 2 researchers undertook qualitative thematic analysis of patient responses. Data were initially coded by a line by line analysis and then key themes identified from the interviews.	
Themes with findings	Patient impact	• Fear • Disbelief • Anger • Frustration • Isolation • Worry about the impact of ADRs on future treatment and job prospects.
	Information	• Seen as responsibility of medical staff
Limitations	• Small study of patients experiencing a variety of serious ADRs and findings may not be representative of wider patient population.	

H.6 Non-specialist management – selective COX-2 inhibitors

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Andri L, Falagiani P. Safety of celecoxib in patients with cutaneous reactions due to ASA-NSAIDs intolerance. Allergologia Et Immunopathologia. 2007; 35(4):126-129[3]	Single blind prospective cohort with 72 hour observation period; single blind study	Original population: n=98 patients (63 women and 35 men) ages 46–69 years (mean age 55.2) were enrolled, all suffering from osteoarthritis with proven intolerance against oral ASA/NSAIDs with phenomena of diffuse erythema or urticaria/angioedema. 86 patients participated in final	Due to the fact that 3 of 32 patients showed urticarial eruptions on the chest and back 2–3 hours after the first administration of 100 mg dose, it was decided to continue with a more progressive schedule (50, 75, 100 mg) in the remaining 54 patients. n=54	Medication dose	Cutaneous reactions	3/32 (9%) patients showed urticarial eruptions on the chest and back 2–3 hours after the first administration of the 100 mg dose. A more progressive schedule	Authors conclude that celecoxib is safe in those with ASA/NSAID intolerance based on a 72 hour observation period.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
		study	54 patients received a progressive dose of Celecoxib			in the remaining 54 patients was adopted. 1/54 (2%) showed urticarial pomphi on the back and chest on day 36	

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Asero R. Etoricoxib challenge in patients with chronic urticaria with NSAID intolerance. Clinical and Experimental Dermatology. 2007; 32(6):661-663.[6]	Prospective comparative cohort; Single blind placebo-controlled oral challenge protocol at least 1 week apart. Tolerance to etoricoxib (only results for this drug relevant to the current	Overall 17 people participated. All received each drug in a random order 1 week apart. 4 men, 13 women; aged 22–74 years with mean age 47 years. Inclusion criteria: A history of recent unequivocal and severe exacerbations of chronic urticaria	History of multiple reactivity.	No stratification or multivariable statistical method applied.	Reactions to drugs – defined as a clear-cut exacerbation of urticaria characterised by a marked increase of pruritus, redness, and number of weals with or without angioedema causing an upgrade of urticarial score	No participant reacted to etoricoxib.	Only frequencies presented – no multivariable adjustments made. Very limited clinical features / prognostic factors presented.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	review here) compared to paracetamol, tramadol (an opiate) and nimesulide (Cox 2 banned in UK) in a group of patients with positive case history of NSAID intolerance.	(defined as the recurrence of hives with or without angioedema) about 20–120 minutes after the ingestion of 1 or more NSAIDs. 11 had a history of reactivity to more than 1 chemically unrelated NSAID Exclusions: children			within 2 hours following the oral challenge.		

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Bavbek S, Celik G, Ozer F, Mungan D, Misirligil Z. Safety of selective COX-2 inhibitors in aspirin/nonsteroidal anti-inflammatory drug-intolerant patients:	Prospective comparative cohort; Single blind placebo-controlled protocol with a 3 day washout period Tolerance to meloxicam compared to	Overall 140 people participated of which 61 received meloxicam. 37 of the overall 140 participants received all 3 drugs. All participants had a history of aspirin or NSAIDs intolerance; study conducted in an outpatient clinic in Ankara (Turkey).	Reactions to multiple analgesics, duration of intolerance, reaction patterns (cutaneous, respiratory), multiple allergies other than to ASA/NSAIDs, comorbid disorders.	No stratification or multivariable statistical method applied.	Reactions to drugs: Urticaria, nasal discharge angioedema, asthma.	Meloxicam 5/61 challenges positive (8.1%) with 2 asthmatic reactions in 2 patients with history of asthmatic reactions to NSAIDs and urticaria-angioedema was detected in	Only frequencies presented – no multivariable adjustments made. No adjustments made for those that received multiple compared to all 3 COX-2 inhibitors, that is, we don't

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
comparison of nimesulide, meloxicam, and rofecoxib. Journal of Asthma. 2004; 41(1):67-75.[9]	rofecoxib (withdrawn over safety concerns) and nimesulide (Cox 2 banned in UK) in a group of patients with positive case history of NSAID intolerance.	20 men, 41 women; aged 16–60 years with mean age 38.4±10.5 years. Inclusion criteria: Patients with a history of ASA/NSAIDs intolerance including asthmatic patients with stable asthma for at least 2 weeks and having a forced expiratory volume value over 70% predicted. Exclusions: Patients taking antihistamines, systemic corticosteroids, cromolyn, sysmpathomimetics, or beta blocker drugs for the last week prior to admittance and having active urticaria or rush.				3 participants, all reactors had multiple analgesic intolerance.	know how many in each group received 1 or all 3 drugs.
					History of asthma and astmatic reactions to NSAIDs.	2 asthmatic reactions in 2 patients with history of asthmatic reactions to NSAIDs.	
					History of multiple analgesic intolerance.	All 5 reactors had multiple analgesic intolerance.	

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Bavbek S, Dursun AB, Dursun E, Eryilmaz A, Misirligil Z. Safety of meloxicam in aspirin-hypersensitive patients with asthma and/or nasal polyps. A challenge-proven study. International Archives of Allergy and Immunology. 2007; 142(1):64-69.[10]	Prospective cohort; single blind placebo controlled oral drug challenge with meloxicam. Numeric results were expressed as means±SE. Nominal variables were expressed as percent of the patients. Patients were challenged with meloxicam and placebo.	21 subjects (11 females, 10 males; mean age (±SE): 38.4 (±2.9) years, range: 16–62 years) were included in the study. 20 patients had nasal polyps. 6 patients had only nasal polyps; 12 patients had associated asthma; 2 patients had associated allergic rhinitis and 1 patient had only asthma. The study was conducted among patients admitted to a tertiary outpatient clinic in Ankara, Turkey. Patients had a history of nasal-ocular symptoms, mild to severe bronchospasm or anaphylactoid reactions within 2 hours after ingesting a prescribed ASA, NSAID, paracetamol or metamizol or a positive response to oral ASA challenge without a history of ASA hypersensitivity.	Clinical symptoms, lung function and blood pressure were monitored.	History of asthma, nasal polyps, or allergic rhinitis.	Rhinorrhea Nasal congestions, Bronchospasm Hoarseness Tongue edema Nausea, vomiting, stomach cramps Hypotension Periorbital swelling Ocular congestion Cough, chest tightness Rhinorehea.	No reaction was observed with placebo and only 1 patient (4.8%) reacted to meloxicam provocation. This patient presented severe bronchial obstruction and generalised erythema during the 20 minutes following the challenge. She had a 7 year history of asthma and nasal polyps and had reacted to ASA challenge.	Meloxicam can be used as a safe alternative for ASA/NSAID.

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Celik G, Pasaoglu G, Bavbek S, Abadoglu O, Dursun B, Mungan D et al. Tolerability of selective cyclooxygenase inhibitor, celecoxib, in patients with analgesic intolerance. Journal of Asthma. 2005; 42(2):127-131.[21]	Prospective comparative cohort; single blind placebo-controlled oral challenge protocol. Study design on 2 separate days 1/4 and 3/4 quarters divided doses of placebo (lactose) and active drug, celecoxib (200 mg) were given with 2 hour intervals, that is stepped up approach or placebo. Conducted in Turkey.	Overall 75 people participated. 20 men/55 women; mean age 38.2 years (SE 1.4). Inclusion criteria: Patients with a history of ASA/NSAIDs intolerance including asthmatic patients with stable asthma for at least 2 weeks and having a forced expiratory volume value over 70% predicted. Exclusions: Patients taking antihistamines, systemic corticosteroids, cromolyn, sysmpathomimetics, or beta blocker drugs for the last week prior to admittance and having active urticaria or rush.	Reactions to multiple analgesics, duration of intolerance, reaction patterns (cutaneous, respiratory), multiple allergies other than to ASA/NSAIDs, comorbid disorders	No stratification or multivariable statistical method applied	Follow-up period 24 hours. Oral challenge test accepted as positive if 1 of the following symptoms existed: Conjuctival reaction; Upper and lower respiratory tract reactions; such as sneezing; Rhinorrhea; Nasal blockage; Dyspnea; Wheezing and cough with a 20% decrease in FEV1; cutaneous reactions such as erythema, pruritus with erythema, urticaria or angioedema; or	No reaction was observed with placebo and celecoxib provocation	Study described a number of baseline characteristics but is not double blinded.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
					anaphylactoid reaction with urticaria; or angioedema and hypotension or laryngeal dema.		

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Colanardi MC, Nettis E, Traetta P, Daprile C, Fitto C, Aloia AM et al. Safety of parecoxib in patients with nonsteroidal anti-inflammatory drug-induced urticaria or angioedema. Annals of Allergy, Asthma and Immunology. 2008; 100(1):82-85.[22]	Prospective cohort; single blind placebo controlled challenge with parecoxib.	79 consecutive patients (44 women and 35 men; mean age 58.7±13.8 years, range 14–68 years) who were referred to the Allergy Clinics of Bari University Hospital, Bari, Italy.	History of cutaneous hypersensitive reactions (urticaria or angioedema) to 1 or more NSAIDs.	Adverse reaction to more than 1 class of NSAIDs.	Urticaria Angioedema	No reaction to placebo was observed in any patient. No reaction to parecoxib was observed in any patients either the single class or multiple class intoleranc e group.	This report demonstrates that parecoxib does not induce cross reactivity in patients with a history of urticaria or angioedema to NSAIDs who require an analgesic drug perioperatively.

2

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Confino-Cohen R, Goldberg A. Safe full-dose one-step nabumetone challenge in patients with nonsteroidal anti-inflammatory drug hypersensitivity. Allergy and Asthma Proceedings. 2003; 24(4):281-284.[24]	Prognostic cohort study; open oral challenge.	24 patients with a history of hypersensitivity reactions to at least 2 different NSAIDs on 2 different occasions; the patients did not suffer from NSAID or ASA induced asthma or urticarial. Ages 20–85 years (mean age 50 years); 19 women and 5 men. Study conducted at the Allergy and Clinical Immunology Unit, Meir General Hospital, Tel Aviv, Israel.	Hypersensitivity reactions to at least 2 different NSAIDs.	NSAID or ASA induced asthma or urticarial.	Urticaria; angioedema; laryngeal edema; hypotension; syncope; wheezing.	22/24 (92%) of patients had no reaction to nabumetone. 1 patient developed a single urticarial lesion on his eyelid 4 hours after commencement of the challenge. Another patient reported mild general pruritis during the night after the challenge.	These results support the possibility that a single full dose of nabumetone can be tried as a safe alternative in most patients with hyper-sensitivity reactions to NSAIDS.

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Domingo MV, Marchuet MJC, Culla MTD, Joanpere RS, Guadano EM.	Prospective cohort study; patients underwent a single blind placebo	108 patients who reported problems with at least 2 NSAIDS or who had a positive oral challenge with ASA	NSAID or ASA sensitivity.	None described.	Urticaria Erythema Angioedema Respiratory symptoms.	Meloxicam was well tolerated by 103/108 (95%)	Meloxicam can be a good option for NSAID intolerant patients.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Meloxicam tolerance in hypersensitivity to nonsteroidal anti-inflammatory drugs. Journal of Investigational Allergology and Clinical Immunology. 2006; 16(6):364-366.[26]	controlled challenge. The total dose was 22.5 mg.	were enrolled. Demographics not provided.				patients. 5/108 (5%) of patients presented with slight urticaria.	

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Dona I, Blanca-Lopez N, Jagemann LR, Torres MJ, Rondon C, Campo P et al. Response to a selective COX-2 inhibitor in patients with urticaria/angi	Prospective cohort; single blind study. Frequencies and chi square analysis for nominal variables and t-tests for interval variables.	252 patients with confirmed skin reactions after taking NSAIDs. There were 151 (60%) women and 101 (40%) men; mean age 39±15.54 years (14–80). 2 patient groups were considered: Group A (n=47) were patients with intolerance to	Patients with intolerance to NSAIDs or intolerance to paracetamol.	Incremental doses. of etoricoxib. Results stratified by Groups A and B as described.	Cutaneous reaction Respiratory symptoms	In Group A of patients with intolerance to NSAIDs and paracetamol, 12/47 patients (25.53%) showed positive response to etoricoxib and in Group	In patients with urticaria and or angioedema with hypersensitivity owing to NSAIDs and cross intolerance to paracetamol, selective COX

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
oedema. induced by nonsteroidal anti-inflammatory drugs. Allergy.: Allergy Service, Carlos Haya Hospital, Malaga, Spain. 2011; 66(11):1428-1433.[27]	were used.	NSAIDs and to paracetamol; Group B (n=50) were patients with intolerance to NSAIDs and good tolerance to paracetamol. 50 of these patients were randomly selected and matched to Group A in age, sex, clinical entity and NSAIDs involved.				B with NSAID sensitivity only 3/50 (6%) showed a positive response to etoricoxib. In all cases the response consisted of mild pruritus and wheals. No patient had any respiratory symptoms.	2 inhibitors may be unsafe.

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
El Miedany Y, Youssef S, Ahmed I, El Gaafary M. Safety of etoricoxib, a specific cyclooxygenase-2 inhibitor, in asthmatic patients with aspirin-	Prospective cohort; single blind placebo controlled study. Frequency distributions were performed.	77 patients with ASA or other NSAID induced asthma, rhinosinusitis and nasal polyps. 31 men and 46 women; mean age 55.9±0.75 years.	ASA or other NSAID induced asthma, rhinosinusitis and nasal polyps.	Incremental doses. of etoricoxib: 60 mg on day 2, 90 mg on day 3 and 120 mg on day 4.	Cutaneous reaction Respiratory symptoms Hypotension Conjunctival reaction Laryngeal edema.	None of 77 study patients experienced any symptoms or developed dyspnoea, change in nasal examination, significant variation in	The results of this study further support the notion that COX 2 specific inhibitors are likely to be safe for use in patients with aspirin exacerbated

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
exacerbated respiratory disease. Annals of Allergy, Asthma and Immunology. 2006; 97(1):105-109.[29]						peak expiratory flow rate greater than 20% or decline in forced expiratory volume. The exact 1 sided confidence interval for the probability of etoricoxib inducting cross reaction in patients with AERD was 0–2%.	respiratory disease.

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Garcia-Rodriguez RM, Hinojosa M, Camacho-Garrido E, Berges Gimeno P, Martin Garcia C. Celecoxib,	Prospective cohort; single blind study; frequency data presented.	20 patients aged 23–72 years. Each had to have 2 or more episodes of urticaria or angioedema following ingestion of at least 2 different NSAIDs.	NSAID hypersensitivity with 2 or more episodes of urticaria or angioedema following ingestion of at least 2 different NSAIDs.	None described	Erythema Urticaria Angioedema Laryngeal edema.	All 20 participants tolerated the celecoxib dosage of 200 mg.	Celecoxib appears to be a safe drug for those with NSAID hypersensitivity.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
safe in NSAID intolerance. Allergy. 2002; 57(11):1085-1086.[39]							

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Goksel O, Aydin O, Misirligil Z, Demirel YS, Bavbek S. Safety of meloxicam in patients with aspirin/non-steroidal anti-inflammatory drug-induced urticaria and angioedema. Journal of Dermatology. 2010; 37(11):973-979.[41]	Prospective cohort; single blind placebo controlled study. Frequency distributions were performed. Univariat analyses performed by Fisher's exact lest and logistic regression for risk factors.	116 patients (86 women and 30 men, mean age 39.6±12.7 years) admitted to Allergy clinic, Ankara University School of Medicine.	All patients had NSAID induced upper respiratory symptoms or angioedema.	Age, sex, comorbid disease, duration of drug allergy, reaction to more than on NSAID. Rate of atopy was 25.9%. Stratified by dose.	Cutaneous reaction Respiratory symptoms Angioedema	No reaction to placebo. 10 of 116 patients (8.6%) developed mild upper respiratory symptoms or angioedema or only erythema or pruritus at 1/4 or cumulative dose of 7.5 mg meloxicam.	The results of this study indicate that 7.5 mg meloxicam is a safe alternative for ASA/NSAID intolerant patients.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J et al. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. Journal of Allergy and Clinical Immunology. 2003; 111(5):1116-1121.[43]	Prospective comparative cohort; 2 phase study first a double blind placebo-controlled cross-over oral challenge protocol 2 occasions 7days apart (10, 30 or 100 mg)followed by an open challenge session as 2 200-mg doses 2 hours apart to test tolerance to celecoxib. Conducted in Sweden, Poland and USA.	Overall 33 people participated. 12men, 21 women; aged 20–70 years with mean age 43.4 years. Inclusion criteria: Asthma and aspirin intolerance with stable asthma with no exacerbations and change in steroid dose during the past 3 months and 6 weeks, respectively. All participants had to have a positive response to challenge with inhaled or oral aspirin within 9 months before the study. Exclusions: Studies with sulphonamide allergy or subjects who had dried COX-2 inhibitors previously.	Unclear.	No stratification or multivariable statistical method applied.	Airway response	No participant had a bronchoconstrictor response.	Study quality somewhat better than that of many other studies since a double blind design was used. However prognostic factors were not clearly tested and only a very limited number of baseline characteristics were reported.
					Nasal response.	No change in nasal symptom scores.	
					Urinary $LTE_{4.}$	No change in urinary LTE4 levels were observed.	
					Other extrapulmonary responses (dermal flush, urticarial or gastrointestinal symptoms.	No other extrapulmonary responses were recorded.	

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Inomata N, Osuna H, Yamaguchi J, Onoda M, Takeshita Y, Chiba Y et al. Safety of selective cyclooxygenase-2 inhibitors and a basic non-steroidal anti-inflammatory drug (NSAID) in Japanese patients with NSAID-induced urticaria and/or angioedema: Comparison of meloxicam, etodolac and tiaramide. Journal of Dermatology. 2007; 34(3):172-177.[52]	Prospective cohort; single blind placebo controlled study. Frequency distributions were performed.	20 Japanese patients (14 women, 6 men; mean age 37.3 years, range 5–76 years) with NSAID induced upper respiratory symptoms or angioedema. Tiramide (does not inhibit Cox).	All patients had NSAID induced upper respiratory symptoms or angioedema.	Multiple NSAID reactors.	Urticaria/angioedema.	No reaction of urticaria/angioedema with placebo was observed. 8/15 (53.3%) of patients receiving etodolac reacted with urticaria/angioedema; 2/6 (33.3%) of patients receiving meloxicam reacted with urticaria/angioedema; 3/14 (21.4%) of patients receiving tiaramide reacted with urticaria/angioedema.	Among the selective Cox 2 inhibitors, meloxicam seems to be better tolerated than etodolac.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Kleinhans M, Linzbach L, Zedlitz S, Kaufmann R, Boehncke WH. Positive patch test reactions to celecoxib may be due to irritation and do not correlate with the results of oral provocation. Contact Dermatitis. 2002; 47(2):100-102.[54]	Prospective comparative cohort;2 phase approach (1) scratch and patch test and (2) single blind placebo-controlled oral challenge protocol. Scratch tests were performed initially and evaluated after 20 minutes and at day 1; patch tests were evaluated at day 2; subsequently they were repeated with diluted celecoxib; oral	Overall 14 people participated. 6 men, 8 women; age (range 18–72). Inclusion criteria: Patients with a history of NSAID sensitivity. Patients were considered to be NSAID sensitive when typical clinical symptoms developed within 6 hours after ingestion of a defined active drug and when compounds (for example, vitamin C) other than the NSAID were subsequently taken without the development of any symptoms. Exclusions: None specified.	History of symptoms (cutaneous 12 patients), respiratory (1 patient), both (1 patient); urticaria (6 patients); number of NSAID sensitivities (5 patients sensitive to 1, 7 patients sensitive to 2, and 2 patients sensitive to more than 2 NSAIDs).	No stratification or multivariable statistical method applied.	Not clearly described but presumably any that were observed with the NSAID sensitivity tests.	No reactions were observed with the celecoxib **scratch test**. 8 out of 10 showed reactions to the **patch test** – erythematous reactions ('+' according to the ICDERG grading system) with decrescendo kinetics between day 2 and 3. 9 patients with no history of NSAID sensitivity reacted in the same way. No reactors with a diluted patch test. No reactors to	Very small study with little description of the baseline characteristics. Study seems to have determined sensitivity upfront and included scratch as well as patch tests.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	provocation was performed single-blind and placebo controlled with increasing doses of celecoxib (50, 100 and 200 mg cumulative 350 mg – in 3 hour intervals). Conducted in Germany.					an oral challenge.	

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Koschel D, Ninck WC, Hoffken G. Tolerability to etoricoxib in patients with aspirin-exacerbated respiratory disease.	Prospective cohort; Single blind placebo controlled challenge. Medical records were retrospectively reviewed and patients	262 patients (108 (41.2%)/male 154 (58.8%) female; median age 51.6 (19–79) had single blind placebo controlled oral challenge with ASA; 122 were positive. Of these 104 had single blind	Aspirin-induced respiratory disease	History of bronchial asthma; history of chronic rhinosinusitis/nasal polyps.	Bronchial, nasal, cutaneous and systemic symptoms.	3/104 (3%) of patients had respire-tory symptoms 101/104 (97%) of patients with ASA sensitivity tolerated etoricoxib.	Etoricoxib is tolerated in most patients with aspirin exacerbated respiratory disease.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Journal of Investigational Allergology and Clinical Immunology. 2013; 23(4):275-280.[55]	with history of NSAID hypersensitivity, asthma and rhinosinusitis /nasal polyps were analysed.	placebo controlled challenge with increasing doses of etoricoxib.					

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Liccardi G, Salzillo A, Piccolo A, Senna G, Piscitelli E, D'Amato M et al. Safety of celecoxib in patients with adverse skin reactions to acetaminophen (paracetamol) and nimesulide associated or not with common	Prospective cohort; single blind placebo controlled oral challenge with Celecoxib.	29 patients enrolled in A. Cardarelli Hospital Allergy Clinic, Naples, Italy. There were 9 male and 20 female; aged 15–68 with mean age 34; all patients had clinical history of adverse reaction to acetaminophen associated with 1 or more NSAID.	Patients with adverse skin reactions to acetaminophen (paracetamol) and some common non-steroidal anti-inflammatory drugs.	Family history of allergy; clinical history of respiratory or food allergy; cutaneous symptoms after the intake of other drugs.	Safety of celecoxib.	None of the patients reacted to placebo. 28 patients (96.5%) tolerated the therapeutic dose of celecoxib (200 mg) without any reaction. 1 person developed moderate angioedema of the lips.	The finding of only 1 positive response (3.4%) to oral challenge with celecoxib in a group of highly reacting patients suggests that this agent has a favourable safety profile.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
non-steroidal anti-inflammatory drugs. European Annals of Allergy and Clinical Immunology. 2005; 37(2):50-53.[63]							

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Llanora GV, Loo EXL, Gerez IF, Cheng YK. Etoricoxib: a safe alternative for NSAID intolerance in Asian patients. Asian Pacific Journal of Allergy and Immunology. 2013; 31(4):330-333[64]	Prospective cohort; blinding unknown; oral provocation test with etoricoxib	74 participants who had been referred to allergy units in 2 hospitals in Singapore for NSAID intolerance; 59% female; mean age 37, 69% Chinese, 12% Malay, 8% Caucasian, 5% Indian, 6% other races; 80% history of intolerance to 1 NSAID, 20% history of intolerance to multiple NSAIDs.	Unclear	Not reported	Etoricoxib tolerance	95% (70/74) of the participants tolerated etoricoxib	The methods section of the study is not comprehensive.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Martin-Garcia C, Hinojosa M, Berges P, Camacho E, Garcia-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. Journal of Investigational Allergology and Clinical Immunology. 2003; 13(1):20-25.[69]	Prospective comparative cohort; single blind placebo-controlled oral challenge protocol Provocation was performed single-blind and placebo controlled with increasing doses of celecoxib (day 1: 50 mg; day 2: 100 mg and 200 mg, in 1 hour intervals). After a wash out period of 1 week a further dose of 200 mg was administered	Overall 33 people with aspirin induced asthma participated. 10 men, 23 women; mean age 55.5 (range 30–70). Inclusion criteria: Patient had to have experienced to or more different documented episodes of asthma attacks following ingestion of at least 2 different NSAIDs. Patients' asthma had to be stable for at least 2 weeks and no respiratory tract infection or allergen exposure for at least 4 weeks prior to the study. Sensitivity based on detailed history and emergency room reports. Exclusions: Patients with a	Length of asthma, aspirin sensitivity to 1 or more NSAIDs; Severity of asthmatic attack after ingestion of NSAID (4 patients required intensive care unit assistance) – according to Global Initiative for Asthma 26 had moderate asthma and 7 severe asthma; Symptoms (rhinoconjunctivitis and asthma and 70% suffered from nasal polyps); concomitant treatment.	No stratification or multivariable statistical method applied	To be accepted as positive 1 of the following had to occur: (1) conjunctival reactions (2) upper or lower respiratory tract reactions (3)cutaneous reactions (4) hypotension (5) laryngeal edema All described in detail in the study.	100% tolerated the 200 mg celecoxib dosage – PEF and spirometric measures before and after challenge did not show significant changes and none of the participants reactions to the placebo or had any side effects such as pyrosis or epigastric pain.	Study described the inclusion criteria in detail and also the reactions that they were intending to look for also objective measures were taken (PEF and sperometric measurements).

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	. All patients remained in hospital for 3 hours after administration of the drug and monitored Conducted in Spain.	forced expiratory volume in 1 second (FEV1) less than 70% of predicted.					

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Mihaela TA, Popescu FD, Mariana V, Florica P. The safety profile of etoricoxib in autoreactive urticaria. Therapeutics, Pharmacology and Clinical Toxicology. 2012; 16(2):116-	Prospective cohort; single blind placebo controlled study. Frequency distributions were performed.	118 patients with history of hypersensitivity to NSAIDs; 98 patients had positive skin test and 20 patients had history of hypersensitivity.	Patients with hypersensitivity to NSAIDs.	Cumulative drug doses.	Urticaria/angio edema.	2 patients (1.69%) developed urticaria in approximately 2 hours after reaching the total dose.	Etoricoxib appears to be well tolerated by patients with a history of hypersensitivity to traditional NSAIDs.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
120.[74]							

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Muratore L, Ventura M, Calogiuri G, Calcagnile F, Quarta E, Muratore M et al. Tolerance to etoricoxib in 37 patients with urticaria and angioedema induced by nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma & Immunology: Official Publication of the American College of Allergy, Asthma, & Immunology.:	Prospective comparative cohort; single blind placebo-controlled oral challenge protocol. Provocation was performed with increasing doses of etoricoxib (day 1: 0.25 mg with an increase of the same dose every 2 hours reaching a final dose of 100 mg; 10 days later: 100 mg twice	Overall 37 people with NSAID sensitivity participated. 17 men/20 women; mean age 34.3. Inclusion criteria: Patients who had experienced at least 3 episodes of urticaria-angioedema syndrome after the ingestion of 2 or more different NSAIDs taken as a single therapeutic agent not associated with other drugs and suspension of treatment with corticosteroids, antihistamines and immunosuppressive agents for at least 7 days.	Unclear since group was not clearly described	No stratification or multivariable statistical method applied	To be accepted as positive if cutaneous or respiratory symptoms developed and patient reported symptoms were noted.	3 (8%) showed diffuse urticaria (none of them had chronic urticaria and had suspended antihistamine use for 14 days). In 2 patients the reaction appeared during the first challenge with a cumulative dose of 75 and 100 mg, respectively. In 1 patient the reaction occurred during the second administration of a cumulative dose of 200 mg.	Study population characteristics not clearly described.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Allergology and Clinical Immunology Service, Vito Fazzi Hospital, Lecce, Italy. 2007; 98(2):168-171.[76]	a day for 2 days). All patients remained in hospital for 24 hours after administration of the drug and monitored. Conducted in Italy.	Exclusions: (1) Clinical history of other different or serious cutaneous adverse reactions and Steven-Johnson syndrome (2) history of generalised urticaria, edema of the glottis, or anaphylactic shock (4) less than 60 days since the last episode of reaction due to aspirin or NSAIDs (5) bronchial asthma, rhinosinusitis, nasal polyposis, chronic urticaria and renal cardiac and liver diseases.					

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Nettis E, Colanardi MC, Ferrannini A, Vacca A, Tursi A. Short-term tolerability of	Prospective comparative cohort; single blind placebo-controlled oral	Overall 141 people with NSAID sensitivity participated. 55 men, 86 women;	Hypersensitive reactions to 1 or more classes of NSAIDs (125 to 1, 14 to 2 and 2 to 3 different classes of NSAIDs);	No stratification or multivariable statistical method applied	To be accepted as positive if cutaneous and mucosal manifestation (erythema, wheals or	2 (1.4%): 1 developed a pruritic rash with itching and the appearance of wheals on the	Larger scale study, but included a more heterogeneous study population compared to

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
etoricoxib in patients with cutaneous hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 2005; 95(5):438-442[79]	challenge protocol Provocation was performed with increasing doses of etoricoxib (day 1: placebo 1 hour apart; day 2 (after a week): 22.5 mg initially and 67.5 mg 1 hour later; 10 days later: 100 mg twice a day for 2 days). All patients remained in hospital for at least 6 hours after administration of the drug with additional visits 24 and	mean age: 37 (SD 17, range 14–74). Inclusion criteria: Well documented data from medical reports regarding cutaneous hypersensitivity reactions to 1 or more NSAIDs Exclusions: Patients who were taking drugs other than the suspected NSAID at the time of the reaction.	Symptomatology (60 patients urticaria alone with 6 additional patients urticaria associated with difficulty in breathing; angioedema alone in 27 patients; urticaria and angioedema in 57 patients exanthematous eruptions in 10 patients; Stevens–Johnson syndrome in 1; fixed erythema in 2; and erythema multiforme in 1); history of atopic disease (19 had a history of at least 1 atopic disease: 12 rhinitis or rhinoconjunctivitis, 4 with food hypersensitivity, bronchial asthma in 2; and atopic dermatitis in 1). 16 patients reported beta-lactam		angioedema) appeared or if or respiratory symptoms or a decrease of at least 20% in BEV1 or hypotension developed.	extremities (person with 2 previous episodes of urticarial eruptions after taking arylprpionics naproxen and ketoprofen respectively); 1 developed a pruritic rash on her hands and wheals subsequently developed on her arms (person with 3 previous episodes of urticarial eruptions after taking aspirin – plus angioedema-, arylprpionics and acetaminophen 22, 7 and 4 months before testing respectively).	other included studies.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	48 hours later to exclude delayed reactions. Conducted in Italy.		hypersensitivity and 5 reported hypersensitivity to other drugs.			Neither experience respiratory symptoms and after treatment with chlorpheniramine maleate symptoms resolved within 2 hours. No patient had adverse reactions to the placebo	

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Nettis E, Di Paola R, Ferrannini A, Tursi A. Meloxicam in hypersensitivity to NSAIDs. Allergy. 2001; 56(8):803-804.[78]	Prospective cohort; single blind placebo controlled per oral challenge with meloxicam.	148 NSAID sensitive patients referred to outpatient department at Department of Clinical Immunology and Allergology, Bari, Italy. There were 53 males and 95 females; mean age 33.9 years (1`6.22 SD); age range 19–79.	Unequivocal history of urticaria with or without angioedema to NSAIDs.	Chronic idiopathic urticaria Immediate or delayed reactions	Cutaneous and mucosal manifestation (erythema or wheals or angioedema).	2/148 (1.35%) showed a positive test. The first subject presented generalised urticaria associated with abdominal pain. The second patient developed diffuse wheals	This study confirms that meloxicam is a tolerable NSAID.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
						and labial edema. Both patients suffered from chronic idiopathic urticaria. No delayed reaction was observed. None of the patients suffered an adverse reaction to placebo.	
					Respiratory symptoms or a decrease of at least 20% in the FEV_1		
					Hypotension		

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Pagani M, Bonadonna P, Dama A, Senna GE, Vescovi PP, Antico A.	Prospective cohort; single blind placebo controlled study.	139 patients with hypersensitivity reactions to 1 or more NSAIDs. M: 37, F: 102;	Hypersensitivity reactions to 1 or more NSAIDs.	Single reactors Reaction to 2 or more NSAIDs Underlying disease.	Safety of etoricoxib Urticaria/angio edema Rhinitis and	4/139 (2.8%) subjects were positive reactors. 3 were single reactors with a	Etoricoxib was well tolerated by NSAID hyper sensitive subjects without

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Long-term tolerability of etoricoxib in different types of NSAID-intolerant subjects. European Annals of Allergy and Clinical Immunology. 2010; 42(6):216-220.[82]		median age of 44 years, range 13–78.83 had history of hypersensitivity to a single NSAID and 56 had hypersensitivity to 2 or more NSAIDs.			asthma Anaphylaxis.	history of NSAID induced cutaneous symptoms who experienced mild urticaria on the face 3 hours after the challenge. 1 patient with multiple NSAID reactions had a severe reaction including generalised urticaria, labial oedema, broncho-spasm and headache 3 hours after challenge. Long term follow-up of 50/52 patients tolerated etoricoxib.	significant differences between single and multiple reactors.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Prieto A, De Barrio M, Martin E,	Prospective cohort; single blind placebo	70 patients intolerant to NSAIDs; 30 patients had asthma	Patients with hypersensitivity to NSAIDs	30 patients had asthma with respiratory	Respiratory symptoms; Cutaneous-	66/70 (94.3%) tolerated 1 g nabumetone	Nabumetone and meloxicam are safe

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Fernandez-Bohorquez M, de Castro FJ, Ruiz FJ et al. Tolerability to nabumetone and meloxicam in patients with nonsteroidal anti-inflammatory drug intolerance. Journal of Allergy and Clinical Immunology. 2007; 119(4):960-964.85	controlled study. Frequency distributions were performed. Fischer exact test were performed to evaluate an difference in tolerance to both drugs between groups A and B.	with respiratory intolerance to NSAIDs (Group A); 40 patients had cutaneous-mucous (urticaria-angioedema) NSAID intolerance (Group B); 37 females and 33 males; age 19–75 years (mean age 43.4 years).		intolerance to NSAIDs; 40 patients had cutaneous-mucous (urticaria-angioedema) NSAID intolerance. Dose level.	mucous symptoms.	(93.3% in group A and 95% in group B). Effects included respiratory symptoms, pruritius, facial erythema and urticaria. At 2 g the tolerability of nabumetone was 83.6%. With respect to meloxicam, 96.1% of patients tolerated 15 mg. No significant difference in nabumetone and meloxicam tolerability was observed between groups A and B.	alternatives in NSAID intolerant patients.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Quaratino D, Romano A,	Prospective cohort; single blind placebo	177 consecutive patients with history of adverse reactions	NSAID sensitive patients.	None described.	Erythema, pruritus accompanied	None of the patients reacted to the	Meloxicam appears to have a very low

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Di Fonso M, Papa G, Perrone MR, D'Ambrosio FP et al. Tolerability of meloxicam in patients with histories of adverse reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 2000; 84(6):613-617.[87]	controlled study. Frequency distributions were performed.	to NSAIDs (47 males and 130 females) ranging in age from 13–83 years (mean 40.33±15.67).			by erythema, urticaria/angio edema, rhinorrhoea, nasal obstruction, sneezing, dyspena, cough associated with a decrease of at least 20% in the FEV_1, hypotension.	placebo challenge .Positive responses to meloxicam challenge were observed in 2 of 177 patients (1.1%). The reactions involved facial oedema and urticaria.	frequency of cross reactivity in patients with histories of urticaria/angioe dema reactions to NSAIDs.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Quiralte J, Delgado J, Saenz de San Pedro B, Lopez-Pascual E, Nieto MA,	Prospective comparative cohort; single blind, placebo-controlled oral challenge protocol.	Overall 33 people with a previous anaphylactoid reaction (AR) to NSAIDs.	Following variables were collected: atopic disease if any; clinical characteristics of the historical	No multivariable statistical method applied.	To be accepted as positive if 1 of the following criteria was met: (1) a 20% decline in the	Celecoxib challenge was performed in 25 patients and was well tolerated in all cases.	With all subjects having had an anaphylactic reaction to an NSAID previously it is probably a more

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Ortega N et al. Safety of the new selective cyclooxygenase type 2 inhibitors rofecoxib and celecoxib in patients with anaphylactoid reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 2004; 93(4):360-364.[88]	Provocation was performed with rofecoxib and celecoxib (results from rofecoxib not reported here). First patients were challenged with the highly selective COX-2 inhibitor rofecoxib or celecoxib. Then successive single blind placebo controlled oral challenges were performed with meloxicam, paracetamol, and at least 1 of: piroxicam, diclofenac, ketoprofen and acetylsalicylic acid. Each oral challenge was carried out separately with at least 7 days between successive challenges (challenges were individualised according to the participants' history. Celecoxib (50, 100 day 1 and 200 mg day 2 challenges with 2 hour intervals) and	14 men, 19 women; mean age 44.8 (range 20–78). Inclusion criteria: Patients who exhibited clinical evidence of an AR after NSAID intake on admission to the emergency department where AR was defined as the presence of urticaria or angioedema plus hypotension (systolic blood pressure <90 mmHg) or largyngeal edema. Exclusions: Not explicitly described.	adverse reaction (the NSAID involved, the dose administered, elapsed time between admininistration of the NSAID and the beginning of the reaction, symptom experienced by the patient, and a previous reaction referred to by the patient) Symptoms involved urticaria and angioedema in all patients, laryngeal edema in 24, systolic hypotension in 13 and the gastrointestinal system in 5. 7 patients had a concomitant atopic disorder (6 had allergic rhinitis and 3 had		FEV1 (2) a naso-ocular reaction (sneezing rhinorrea, nasal blockage and conjunctival injection); (3) pruritic and erythematous areas raised over normal skin; (4) macular or popular areas in any localisation; (5) swelling of the skin or external mucosa and (6) AR (urticaria or angioedema plus hypotension or laryngeal edema).		severe population compared to other papers.
						No delayed reactions or reactions to placebo were observed.	

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	meloxicam (7.5 and 15 mg with 60 minutes interval). All patients remained in hospital for at least 2 hours after administration of the drug with a follow-up after 24 hours). Conducted in Italy.		bronchial asthma caused by inhalant allergens).				

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Roll A, Wuthrich B, Schmid-Grendelmeier P, Hofbauer G, Ballmer-Weber BK. Tolerance to celecoxib in patients with a history of adverse reactions to nonsteroidal anti-	Prospective comparative cohort; single blinded drug challenge protocol. Tolerance to celecoxib compared to paracetamol and nimesulide (Cox 2 banned in UK) in a	106 patients with history of NSAID intolerance from Allergy Unit at University Hospital Zurich. 33 men, 73 women; aged 13–76 years with mean age 41.7±11.7 years.	History of NSAID intolerance.	History of asthma Polyposis (polyps) Atopic diseases Urticaria.	Positive oral challenge including cutaneous and respiratory reactions, angioedema	Celecoxib 5/106 challenges positive (4.7%) with 2 angioedema, 2 generalised puritis and 1 generalised with thoracic oppression. None of the asthmatic patients reacted to	Celecoxib is an appropriate alternative drug with an excellent tolerance in subjects with a history of adverse reactions to ASA or to other NSAIDs confirming the low rate of cross

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
inflammatory drugs. Swiss Medical Weekly. 2006; 136(43-44):684-690.[89]	group of patients with positive case history of NSAID intolerance.					celecoxib.	intolerance of this Cox 2 specific drug with other NSAIDs.

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Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Cuatneous hypersenisitvity reactions to inhibitors of cyclooxygenase-2. Clinical Trends. 2007; 19:44-49.[91]	Prospective comparative cohort; single blind, placebo-controlled oral challenge protocol (drugs concealed in identical opaque capsules. Provocation was performed with half doses 1 hour apart (maximal	Overall 206 people with NSAID sensitivity participated. n=39 single reactors and n=167 crossreactors. 62 men/144 women; mean age 31.1 (sd 13.7). Inclusion criteria: Patients with a history of urticaria or angioedema triggered by NSAIDs whose hypersensitivity was confirmed with a challenge test at the outset of the study.	Baseline characteristics were provided according to single and crossreactos, as well as atopic disease, asthma, rhinitis, dermatitis	Even though patients were stratification results were not divided by these groupings or multivariable statistical method applied.	No clear description / definition was provided how hypersensitivity was defined. It was only stated that positive oral challenges were manifested as facial angioedema or urticarial.	14/76 (18.4%) reacted to celecoxib; 7/62 (11.2%) reacted to etoricoxib; and 6/29 (20.6%) to meloxicam. Severity not described.	Seems to have a higher rate of reactors than most other studies and there were. It was also unclear whether this study is including participants from the 2005 study. Various numbers do not match up.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	dose of meloxicam 15 mg and celecoxib 200 mg and etoricoxib 120 mg). All patients remained in hospital for at least 3 hours after administration of the drug with a telephone follow-up after 24 hours). Washout period not described. Table 2 in paper has numbers of patients mixed-up and these numbers are different in the methods.	Exclusions: Patients with aspirin-exacerbated respiratory disease (aspirin-intolerant asthma).					

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
	Conducted in Venezuela.						

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Senna GE, Passalacqua G, Dama A, Crivellaro M, Schiappoli M, Bonadonna P et al. Nimesulide and meloxicam are a safe alternative drugs for patients intolerant to nonsteroidal anti-inflammatory drugs. European Annals of Allergy and Clinical Immunology. 2003; 35(10):393-	Prospective cohort; single blind placebo controlled study. Frequency distributions were performed.	381 patients (118 male, 263 female, mean age 53.2 years) with well documented pseudo-allergic reaction to NSAIDs. All patients were given nimesulide and 88 were also give meloxicam.	Patients with pseudo-allergic reaction due to a single or multiple NSAID.	Reactions to Nimesulide (not approved in UK) Meloxicam Dose.	Cutaneous symptom Respiratory symptoms.	Meloxicam: 95.4% tolerated meloxicam. These 4 patients positive to meloxicam had a generalised urticaria (1 with 7.5 mg and 3 with 15 mg). In patients who took meloxicam after challenge no pseudo-allergic reaction occurred.	Meloxicam is a safe and reliable alternative for patients with pseudo-allergic reactions to ASA and NSAIDs.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
396.[97]							

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Senna G, Bilo MB, Antonicelli L, Schiappoli M, Crivellaro MA, Bonadonna P et al. Tolerability of three selective cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib and rofecoxib in NSAID-sensitive patients. European Annals of Allergy and Clinical Immunology. 2004;	Prospective comparative cohort; single blind, placebo-controlled oral challenge protocol. Provocation was performed with meloxicam, rofecoxib and celecoxib (results from rofecoxib not reported here). All patients remained in hospital for at least 2	Overall 76 people with NSAID sensitivity participated. Stratified according to 3 categories: n=24 patients with NSAID induced rhinitis and asthma (group A) 8 men, 16 women; mean age 51.1 (range 34–79); n=34 patients with multiple drug induced urticaria or angioedema (group B) 11 men, 23 women; mean age 45.9 (range 16–75) and n=18 NSAIDs induced urticaria or angioedema 6 men, 12 women; mean age 54.7 (range	According to stratified groups.	No multivariable statistical method applied.	To be accepted as positive in asymptomatic patients (group A and B) if 1 of the following occurred: (1) erthyema, urticaria or angioedema, rhinorrea, nasal obstruction, sneezing dyspnea or cough associated with a fall of FEV1>20% of the baseline, and hypotension For those in participants with urticaria a test was	4/72 (6.56%) reacted to celecoxib (2 from group B and 2 from group C) and 3/73 (4.1%) reacted to meloxicam (1 from group B and 2 from group C). No delayed reactions or reactions to placebo were observed.	It seems that at least some prior predictions were made since subjects were grouped into 3 categories. However all 3 drugs seemed to have been administered on the same day with a 2-hour interval.

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
36(6):215-218.[96]	hours after administration of the drug with a follow-up after 24 hours). Conducted in Italy.	32–72). Inclusion criteria: Patients with a history of at least 2 previous pseudo-allergic reactions to NSAIDs 1 of them occurred during the past 12 months; a documented relationship between the intake of the drug and the onset of symptoms (no more than 12 hours); a single NSAID drug was taken before each episode. Exclusions: Patients with significant active medical conditions (pulmonary, gastro-intestinal, cardiovascular, psychiatric, hepatic, neurologic, renal or haematologic).			considered positive if there was an increase of urticarial lesions of >30% of the body surface.		

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Valero A, Sanchez-Lopez J, Bartra J, Serrano C, Munoz-Cano R, Roca J et al. Safety of parecoxib in asthmatic patients with aspirin-exacerbated respiratory disease. International Archives of Allergy and Immunology. 2011; 156(2):221-223[107]	Prospective cohort study; study was placebo controlled but blinding not described. Results measured as frequencies.	10 patients (7 women and 3 men, 53.8±9 years old) who were referred to the Pneumology and Respiratory Allergy Department of the Hospital Clinic in Barcelona, Spain for asthma exacerbations precipitated by 2 or more different NSAIDs. All patients also had polyposis and asthma. All patients had tolerated celecoxib in a previous study.	Asthma patients with aspirin exacerbated respiratory disease and polyposis. Previously tolerated celecoxib. Dose.		Urticaria/angio edema.	No symptoms were reported with any of the administered doses and there were no signs of immediate or delayed hyper-sensitivity.	Parecoxib was well tolerated by all the patients in this study with no adverse reactions and could be a safe alternative in NSAID intolerant patients.
					FEV_1 decrease >20% of baseline.		
					Acoustic rhinometry decrease >30% of baseline		
					Late asthmatic response assessed by a >30% decrease in peak expiratory flow.		
					Late cutaneous reaction.		

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Viola M, Quaratino D,	Prospective single blind	120 NSAID sensitive patients (83 women	NSAID sensitivity.	Reactions to more than 1 NSAID.	Cutaneous symptoms.	None of the patients	Celecoxib was well tolerated in

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Gaeta F, Caringi M, Valluzzi R, Caruso C et al. Celecoxib tolerability in patients with hypersensitivity (mainly cutaneous reactions) to nonsteroidal anti-inflammatory drugs. International Archives of Allergy and Immunology. 2005; 137(2):145-150.[110]	placebo controlled cohort study; analysis by frequency data only.	and 37 men, ranging in age from 18 to 86 years, mean age 45.0±16.5 years). Patients were seen in Allergy Unit, UCSC, Rome.				developed symptoms after administration of the placebo. A skin reaction to the celecoxib challenge was observed in 1/120 patients (0.8%).	patients with NSAID related respiratory symptoms.
					Respiratory symptoms.		

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Viola M, Quaratino D, Gaeta F, Caruso C, Valluzzi R, Romano A. Etoricoxib	Single blind placebo controlled prospective cohort study; frequency	31 adults (21 women and 10 men) ranging in age from 23–71 years (mean age 42.9±16.4) and reporting 1 or more adverse reactions to	Patients with well-established NSAID hypersensitivity.	More than 1 NSAID hypersensitivity; History of bronchial asthma or rhinitis.	Cutaneous reaction.	None of the patients experienced symptoms after administration of either	Etoricoxib seems to be a safe alternative for patients with allergic and non-allergic hyper-

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
tolerability in patients with hypersensitivity to nonsteroidal anti-inflammatory drugs. International Archives of Allergy and Immunology. 2007; 143(2):103-108.[111]	analysis.	NSAIDs evaluated in the allergy units of Complesso Integrato Columbus and Oasi Maria Santissima, Italy. No history of nasal polyps in any patients.			 Respiratory symptoms.	placebo or etoricoxib.	sensitivity to NSAIDs. Etoricoxib was tolerated at highest dose of 120 mg.

1

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
Woessner KM, Simon RA, Stevenson DD. The safety of celecoxib in patients with aspirin-sensitive asthma. Arthritis and Rheumatism. 2002;	Double blind prospective cohort study; frequency data provided and 1 sided 95% CI for probability of cross reaction.	60 patients with asthma who believed they were ASA/NSAID sensitive volunteered to enter this study. Their average was 45 years; 34 women and 26 men were included. Scripps Research Institute, La Jolla, California.	ASA sensitive patients with asthma (all 60 patients proven to have ASA sensitivity).	Dose of drug: 100 mg and 200 mg celecoxib. Concomitant drugs, particularly systemic corticosteroids and leukotriene modifiers.	Respiratory symptoms.	There were no reactions to celecoxib at either dose and only 1 placebo reaction due to irritation from contact lens solution. All patients reacted to ASA. The 1 sided 95% CI for the underlying	This study supports the notion that COX 1 inhibition plays a role in precipitation of severe asthma attacks in asthma exacerbated respiratory disease and demonstrates the safety of the

Reference	Study type and analysis	Number of participants and characteristics	Prognostic variable(s)	Confounders OR stratification strategy	Outcome measures	Effect sizes	Comments
46(8):2201-2206.[113]						probability of celecoxib inducting respire-tory cross reactions in patients with asthma exacerbated respirator disease was between 0–0.05 or 0–5%.	COX 2 selective inhibitor celecoxib in asthmatic individuals.

H.7 Referral to specialist drug allergy services

H.7.1 Beta-lactam antibiotics

Reference	Study type	Number of patients	Patient characteristics	Intervention and comparison	Outcome measures	Effect sizes	Comments
Frigas E, Park MA, Narr BJ, Volcheck GW, Danielson DR, Markus PJ et al. Preoperative evaluation of patients with history of	Study type: Cohort Data source: Mayo Clinic screening through Preoperation Evaluation Clinic (POEC) or Preoperative evaluation settings (OPES). Patient records retrieved for information on preoperative	n=416 at the POEC; 69 patients at OPES. Inclusion criteria: Patients with history of allergy to penicillin (HOAP) who were scheduled for elective surgery and required a decision re which antibiotic to use for preoperative antibiotic prophylaxis (POABP).	Male: Female and Mean Age See table below	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 other preoperative evaluation settings (OPES) where there was no consultation or	Rates of antibiotic use	See table below	Source of funding: Grant from Mayo Clinic No patients were skin test positive. There was a significant increase in the use of cephalosporin and decrease in

allergy to penicillin: comparison of 2 models of practice. Mayo Clinic Proceedings Mayo Clinic. 2008; 83(6):651-662[37]	antibiotic use and any adverse reactions attributed to it. Setting: See above Country: USA Recruitment: Of the 4889 patients screened at the POEC in the first half of 2004, the first 412 consecutive patients with HOAP were studied. Of the first 416 patients screened in 2004 at OPES, the first 69 consecutive patients with HOAP were included in the study.	Exclusion criteria: Patients with a history of life-threatening reaction to penicillin or with HOAP that was indicative of non-IgE mediated reactions (exfoliative dermatitis, mucosal lesions, liver or kidney damage or haemolytic anaemia) did not receive a skin test: instead a non-beta-lactam was recommended for POABP.		testing.			the use of vancomycin in the model of practice that uses an allergy consultation and skin testing in the selection of the antibiotic compared with the model that does not. Negative skin tests did not preclude use of alternative drugs.

Characteristic	**History of allergy to beta-lactams**		**HOAP specifically**	
	Screened at POEC n=412	Screened at OPES n=69	Screened at POEC n=365	Screened at OPES n=46
Age (y) Mean±SD	60±15	63±18	60±15	66±17
Sex Female	239 (58%)	42 (61%)	201 (55%)	26 (57%)

Male	173 (42%)	27 (39%)	164 (45%)	20 (43%)
Antibiotic Administered for POABP in Patients with HOAP, Evaluated at POEC versus OPES				
Antibiotic given for POABP	History of allergy to beta-lactams		HOAP specifically	
	Screened at POEC n=412	Screened at OPES n=69	Screened at POEC n=365	Screened at OPES n=46
Cephalosporin	280 (68%)	23 (33%)	254 (70%)	18 (39%)
Vancomycin	42 (10%)	18 (26%)	36 (10%)	13 (28%)
Other	90 (22%)	28(41%)	75 (21%)	15 (33%)

H.7.2 NSAIDs

There are no clinical evidence tables for this review.

H.7.3 Local anaesthetics

There are no clinical evidence tables for this review.

H.7.4 General anaesthesia

There are no clinical evidence tables for this review.

Appendix I: Economic evidence tables

There are no economic evidence tables for this guideline.

Appendix J: Forest plots

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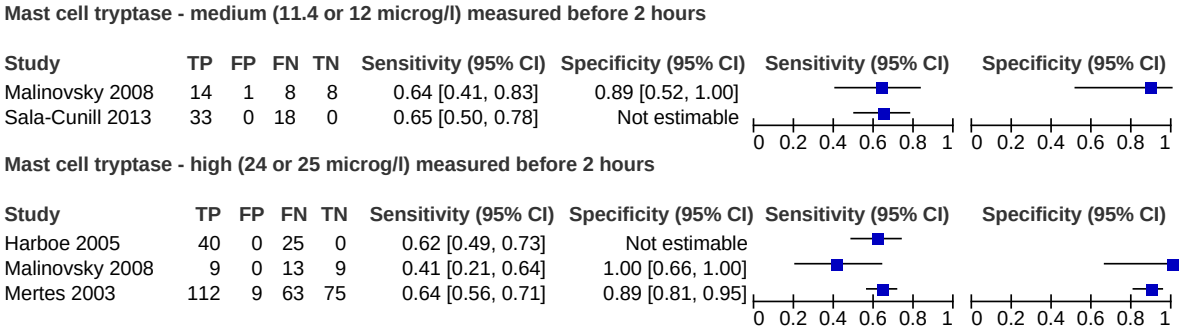
J.1 Assessment

There were no forest plots for this review.

J.2 Measuring serum tryptase after suspected anaphylaxis

Figure 9: Serum tryptase testing: paired sensitivity and specificity at medium and high tryptase thresholds

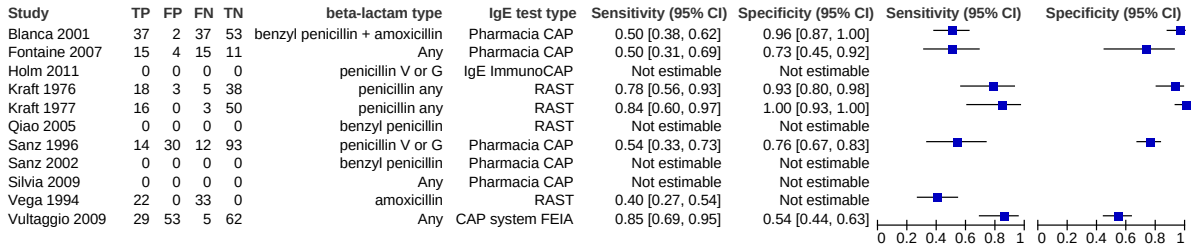


Note: for Harboe et al. 2005 and Sala-Cunill et al. 2013 the population consisted of people with anaphylaxis only and therefore specificity could not be calculated.

J.3 Measuring serum specific IgE

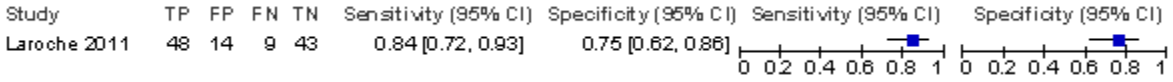
J.3.1 Beta-lactam antibiotics

Figure 10: Serum IgE for identifying reactions to beta-lactam antibiotics: paired sensitivity and specificity



J.3.2 Neuromuscular blocking agents

Figure 11: Serum IgE for identifying reactions to neuromuscular blocking agents: paired sensitivity and specificity



J.4 Documenting and sharing information with other healthcare professionals

There are no forest plots for this review.

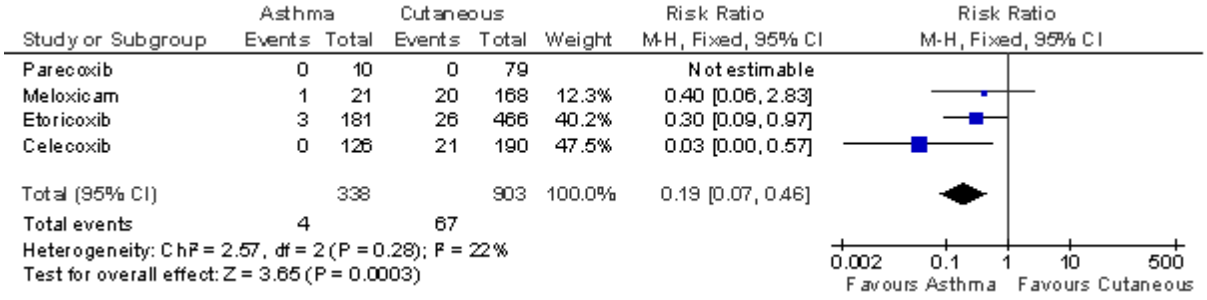
J.5 Providing information and support to patients

There are no forest plots for this review.

J.6 Non-specialist management – selective COX-2 inhibitors

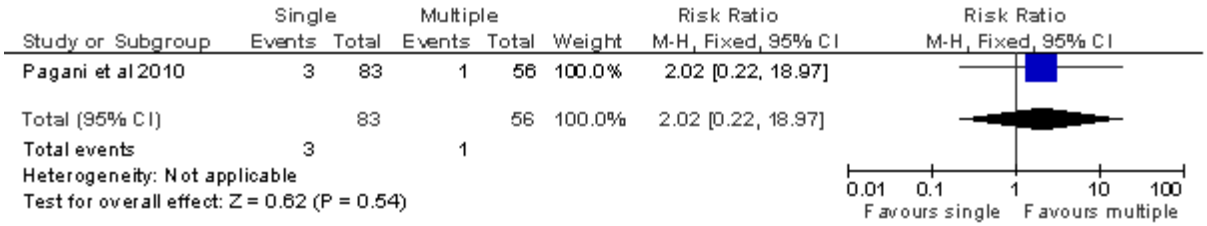
J.6.1 Prognostic factor: history of asthmatic reaction versus cutaneous reaction

Figure 12: Rate of drug reactions to selective COX-2 inhibitors by history of asthma exacerbated by NSAIDs versus history of cutaneous reactions to NSAIDs



J.6.2 Prognostic factor: history of allergic reactions to single NSAID versus multiple NSAIDs

Figure 13: Rate of drug reactions to selective COX-2 inhibitors for people with a history of previous allergic reactions to a single NSAID versus multiple NSAIDs



J.7 Referral to specialist drug allergy services

J.7.1 Beta-lactam antibiotics

Figure 14: Cephalosporin use for perioperative antibacterial prophylaxis (patients with suspected previous allergy to any beta-lactam): 'Preoperative Evaluation Clinic' (POEC) setting versus 'Other non-POEC' (OPES) setting

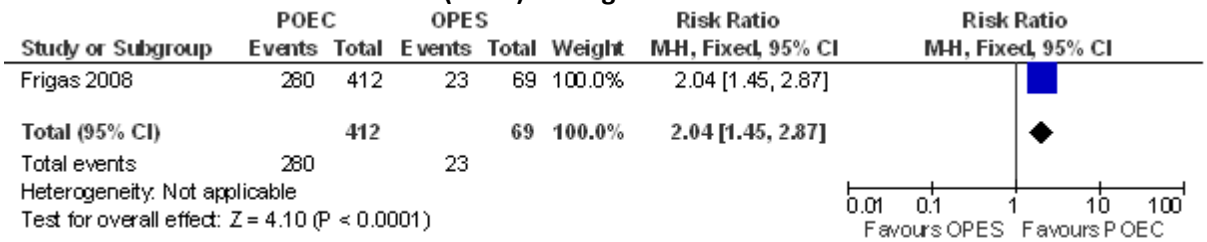


Figure 15: Vancomycin use for perioperative antibacterial prophylaxis (patients with suspected previous allergy to any beta-lactam): 'Preoperative Evaluation Clinic' (POEC) setting versus 'Other non-POEC' (OPES) setting

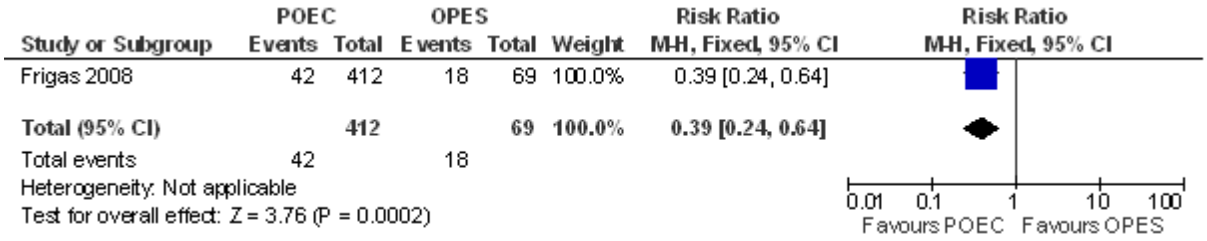


Figure 16: Cephalosporin use for perioperative antibacterial prophylaxis (patients with suspected previous allergy to penicillin): 'Preoperative Evaluation Clinic' (POEC) setting versus 'Other non-POEC' (OPES) setting

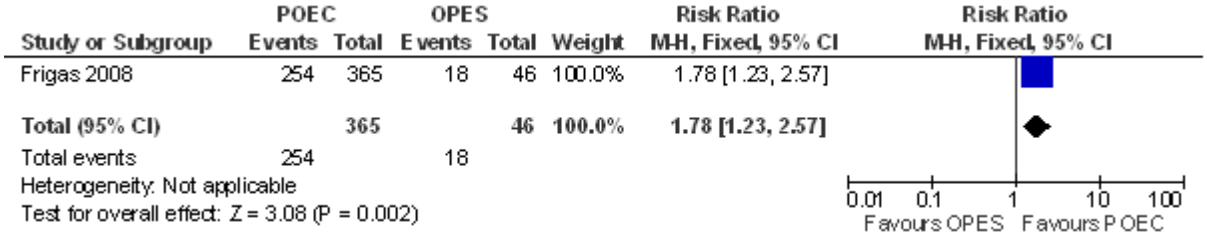
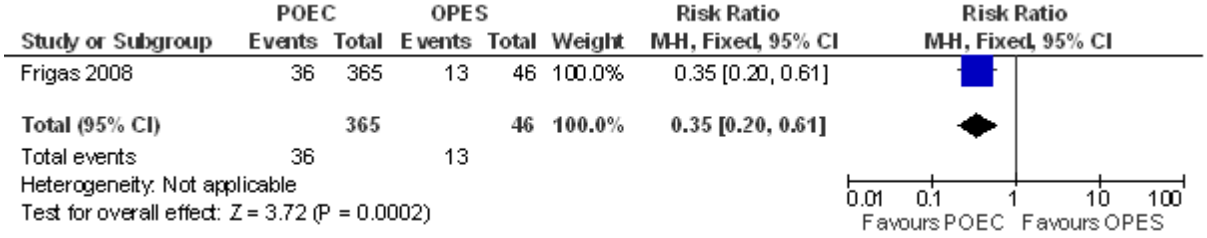


Figure 17: Vancomycin use for perioperative antibacterial prophylaxis (patients with suspected previous allergy to penicillin): 'Preoperative Evaluation Clinic' (POEC) setting versus 'Other non-POEC' (OPES) setting



J.7.2 NSAIDs

There are no forest plots for this review.

J.7.3 Local anaesthetics

There are no forest plots for this review.

J.7.4 General anaesthesia

There are no forest plots for this review.

Appendix K: Excluded clinical studies

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K.1 Assessment

Reference	Reason for exclusion
Avner M, Finkelstein Y, Hackam D, Koren G. Establishing causality in pediatric adverse drug reactions: Use of the Naranjo probability scale. Pediatric Drugs. 2007; 9(4):267-270	Case study. No new algorithm presented
Benahmed S, Picot MC, Dumas F, Demoly P. Accuracy of a pharmacovigilance algorithm in diagnosing drug hypersensitivity reactions. Archives of Internal Medicine. 2005; 165(13):1500-1505	No new algorithm presented or already in systematic review
Bernal Y, Montane E, Barriocanal A, Arellano AL, Garcia F, Costa J. Causality assessment of adverse drug reactions: Comparison of three methods. Basic and Clinical Pharmacology and Toxicology. 2012; 111:21	Abstract only
Bernonille S, Nies J, Pedersen HG, Guillot B, Maazi M, Berg AL et al. Three different cases of exploiting decision support services for adverse drug event prevention. Studies in Health Technology and Informatics. 2011; 166:180-188	Ordered in relation to documentation rerun – descriptive no effectiveness data
Berry LL, Segal R, Sherrin TP, Fudge KA. Sensitivity and specificity of three methods of detecting adverse drug reactions. American Journal of Hospital Pharmacy. 1988; 45(7):1534-1539	No new algorithm. Statistical methods only
Bircher AJ. Symptoms and danger signs in acute drug hypersensitivity. Toxicology. 2005; 209(2):201-207	Risk factors and history taking. No algorithm
Brown S, Black K, Mrochek S, Wood A, Bess T, Cobb J et al. RADARx: Recognizing, Assessing, and Documenting Adverse Rx events. Proceedings. 2000;101-105	See documentation rerun
Cantor MN, Feldman HJ, Triola MM. Using trigger phrases to detect adverse drug reactions in ambulatory care notes. Quality and Safety in Health Care. 2007; 16(2):132-134	No new algorithm
Case B, Oszko MA. Use of an algorithm to evaluate published reports of adverse drug reactions. American Journal of Hospital Pharmacy. 1991; 48(1):121-122	No new algorithm presented or already in systematic review
Castle W. Adverse drug reactions: Scope and limitations of causality assessment and the use of algorithms. International Journal of Risk and Safety in Medicine. 1991; 2(4):185-191	Narrative review
Celik G, Aydyn O, Dogu F, Cipe F, Boyvat A, Ikinciogullari A et al. An algorithmic evaluation of beta-lactam antibiotic allergy. Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:408-409	Abstract only
Confino-Cohen R, Leader A, Klein N, Pereg D, Khoury S, Perl L et al. Drug allergy in hospitalized patients: the contribution of allergy consultation and a structured questionnaire. International Archives of Allergy and Immunology. 2012; 158(3):307-312	Naranjo scale applied to all questionnaires.
Cornu P, Steurbaut S, De BM, Putman K, Van D, V, Dupont AG. Clinical decision support systems in hospitals: What do physicians expect? International Journal of Clinical Pharmacy. 2013; 35(5 SUPPL. 2):943	Conference abstract: fully published evidence sufficiently available
De Vries ST, Mol PGM, De ZD, Haaijer-Ruskamp FM, Denig P. Development and Initial Validation of a Patient-Reported Adverse Drug Event Questionnaire. Drug Safety. 2013; 36(9):765-777	Patient rather than physician questionnaire. Drug allergy also not analysed separately
Doherty MJ. Algorithms for assessing the probability of an Adverse Drug Reaction. Respiratory Medicine CME. 2009; 2(2):63-67	Narrative review
Dormann H, Criegee-Rieck M, Neubert A, Egger T, Levy M, Hahn EG et al. Implementation of a computer-assisted monitoring system for the detection of adverse drug reactions in gastroenterology. Alimentary Pharmacology and Therapeutics. 2004; 19(3):303-309	Use of Naranjo scale
Du Toit G, Lloyd K, Sinnott L, Forster D, Austin M, Clark C et al. The RCPCH care	Specifics of history

Reference	Reason for exclusion
pathway for children with drug allergies: An evidence and consensus based national approach. Archives of Disease in Childhood. 2011; 96(SUPPL. 2):i15-i18	taking not included
Epstein RH, St Jacques P, Stockin M, Rothman B, Ehrenfeld JM, Denny JC. Automated identification of drug and food allergies entered using non-standard terminology. Journal of the American Medical Informatics Association. 2013; 20(5):962-968	Ordered in relation to documentation rerun – descriptive no effectiveness data
Forster AJ, Jennings A, Chow C, Leeder C, van Walraven C. A systematic review to evaluate the accuracy of electronic adverse drug event detection. Journal of the American Medical Informatics Association. 2012; 19(1):31-38	Electronic systems evaluated for detection of electronic triggers using information systems
Frick PA, Cohen LG, Rovers JP. Algorithms used in adverse drug event reports: A comparative study. Annals of Pharmacotherapy. 1997; 31(2):164-167	Karch algorithm does not include drug allergy
Garcia-Cortes M, Lucena MI, Pachkoria K, Borraz Y, Hidalgo R, Andrade RJ et al. Evaluation of naranjo adverse drug reactions probability scale in causality assessment of drug-induced liver injury. Alimentary Pharmacology and Therapeutics. 2008; 27(9):780-789	Not drug allergy
Girard M. Testing the methods of assessment for adverse drug reactions. Adverse Drug Reactions and Acute Poisoning Review. 1984; 3(4):237-244	Narrative review
Goh CL. An approach to the evaluation and documentation of adverse drug reaction. Singapore Medical Journal. 1989; 30(3):285-289	Narrative description
Hakkarainen KM, Andersson Sundell K, Petzold M, Hagg S. Methods for assessing the preventability of adverse drug events: a systematic review. Drug Safety. 2012; 35(2):105-126	Prevention of ADRs – not topic of interest
Hammann F, Gutmann H, Vogt N, Helma C, Drewe J. Prediction of adverse drug reactions using decision tree modeling. Clinical Pharmacology and Therapeutics. 2010; 88(1):52-59	Properties of compounds that predispose them to cause ADRs – not topic of interest
Hauben M, Reich L. Potential utility of data-mining algorithms for early detection of potentially fatal/disabling adverse drug reactions: a retrospective evaluation. Journal of Clinical Pharmacology. 2005; 45(4):378-384	Use of data mining algorithms – not topic of interest
Heelan K, Shear NH. Cutaneous drug reactions in children: an update. Paediatric Drugs. 2013; 15(6):493-503	Not an algorithm, but rather a description of symptoms
Heinzerling LM, Tomsitz D, Anliker MD. Is drug allergy less prevalent than previously assumed? A 5-year analysis. British Journal of Dermatology. 2012; 166(1):107-114	No algorithm presented
Hemens BJ, Holbrook A, Tonkin M, Mackay JA, Weise-Kelly L, Navarro T et al. Computerized clinical decision support systems for drug prescribing and management: a decision-maker-researcher partnership systematic review. Implementation Science. 2011; 6:89	Drug therapy management – not question of interest
Hohl CM, Yu E, Hunte GS, Brubacher JR, Hosseini F, Argent CP et al. Clinical decision rules to improve the detection of adverse drug events in Emergency Department patients. Academic Emergency Medicine. 2012; 19(6):640-649	Time and drug too unspecific
Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. Annals of Pharmacotherapy. 2007; 41(4):674-680	ADR rather than allergy
Hume AL, Quilliam BJ, Goldman R, Eaton C, Lapane KL. Alternatives to potentially inappropriate medications for use in e-prescribing software: triggers and treatment algorithms. BMJ Quality and Safety. 2011; 20(10):875-884	See documentation rerun
Hutchinson TA, Flegel KM, Kramer MS, Leduc DG, Kong HH. Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective	Kramer algorithm already in systematic

Reference	Reason for exclusion
study. Journal of Chronic Diseases. 1986; 39(7):533-542	review
Hutchinson TA, Lane DA. Assessing methods for causality assessment of suspected adverse drug reactions. Journal of Clinical Epidemiology. 1989; 42(1):5-16	Kramer algorithm already in systematic review
Hutchinson TA, Lane DA. Standardized methods of causality assessment for suspected adverse drug reactions. Journal of Chronic Diseases. 1986; 39(11):857-860	Commentary – algorithm not presented
Hwang S-H, Lee S, Koo H-K, Kim Y. Evaluation of a computer-based adverse-drug-event monitor. American Journal of Health-System Pharmacy. 2008; 65(23):2265-2272	Route of administering an algorithm rather than a new algorithm
Jani YH, Barber N, Wong ICK. Characteristics of clinical decision support alert overrides in an electronic prescribing system at a tertiary care paediatric hospital. International Journal of Pharmacy Practice. 2011; 19(5):363-366	Electronic prescribing – not topic of interest
Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1977; 21(3):247-254	ADRs only – drug allergy not included
Kilbridge PM, Alexander L, Ahmad A. Implementation of a system for computerized adverse drug event surveillance and intervention at an Academic Medical Center. Journal of Clinical Outcomes Management. 2006; 13(2):94-100	See documentation rerun
Kilbridge PM, Noirot LA, Reichley RM, Berchelmann KM, Schneider C, Heard KM et al. Computerized surveillance for adverse drug events in a pediatric hospital. Journal of the American Medical Informatics Association. 2009; 16(5):607-612	See documentation rerun
Kitaguchi T, Nohiri T, Suzuki S. Some assesment systems for industry post marketing adverse drug reaction (ADR) information. Iyakuhin Kenkyu. 1983; 14:980-982	Japanese language
Koh Y, Shu CL. A new algorithm to identify the causality of adverse drug reactions. Drug Safety. 2005; 28(12):1159-1161	Included in systematic review
Koh Y, Yap CW, Li SC. Development of a combined system for identification and classification of adverse drug reactions: Alerts Based on ADR Causality and Severity (ABACUS). Journal of the American Medical Informatics Association. 2010; 17(6):720-722	Update of previous paper which was included
Koh Y, Yap CW, Li SC. A quantitative approach of using genetic algorithm in designing a probability scoring system of an adverse drug reaction assessment system. International Journal of Medical Informatics. 2008; 77(6):421-430	No new algorithm presented or already in systematic review
Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs). Position Paper of the EAACI Task Force on Hypersensitivity to Non-Steroidal Anti-inflammatory Drugs. Allergy. 2011;	Position paper
Kramer MS, Hutchinson TA. The Yale algorithm. Special workshop--clinical. Drug Information Journal. 1984; 18(3-4):283-291	Kramer algorithm already in systematic review
Kuo MH, Kushniruk AW, Borycki EM, Greig D. Application of the Apriori algorithm for adverse drug reaction detection. Studies in Health Technology and Informatics. 2009; 148:95-101	Not applied to drug allergy
Lanctot KL, Naranjo CA. Comparison of the Bayesian approach and a simple algorithm for assessment of adverse drug events. Clinical Pharmacology and Therapeutics. 1995; 58(6):692-698	No new algorithm presented or already in systematic review
Lane DA, Kramer MS, Hutchinson TA, Jones JK, Naranjo C. The causality assessment of adverse drug reactions using a Bayesian approach. Pharmaceutical Medicine. 1987; 2(3):265-283	Kramer and Naranjo already in systematic review
Leventhal JM, Hutchinson TA, Kramer MS, Feinstein AR. An algorithm for the	Kramer algorithm

Reference	Reason for exclusion
operational assessment of adverse drug reactions. III. Results of tests among clinicians. JAMA. 1979; 242(18):1991-1994	already in systematic review
Lindquist M, Stahl M, Bate A, Edwards IR, Meyboom RH. A retrospective evaluation of a data mining approach to aid finding new adverse drug reaction signals in the WHO international database. Drug Safety. 2000; 23(6):533-542	Statistical methods – not topic of interest
Loupi E, Ponchon AC, Ventre JJ, Evreux JC. [Imputability of a teratogenic effect]. Therapie. 1986; 41(3):207-210	No applied to drug allergy
Macedo AF, Marques FB, Ribeiro CF, Teixeira F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability. Journal of Clinical Pharmacy and Therapeutics. 2003; 28(2):137-143	No new algorithm presented or already in systematic review
Macedo AF, Marques FB, Ribeiro CF. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? Drug Safety. 2006; 29(8):697-702	No new algorithm presented or already in systematic review
Machado D, Gomes E. Are pharmacovigilance algorithms trustful for the diagnosis of drug hypersensitivity? European Annals of Allergy and Clinical Immunology. 2010; 42(2):53	Abstract only
Mangoni AA. Predicting and detecting adverse drug reactions in old age: challenges and opportunities. Expert Opinion on Drug Metabolism and Toxicology. 2012; 8(5):527-530	Narrative review
Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology. 1997; 26:664-669	Not drug allergy
Matsushita Y, Kuroda Y, Niwa S, Sonehara S, Hamada C, Yoshimura I. Criteria revision and performance comparison of three methods of signal detection applied to the spontaneous reporting database of a pharmaceutical manufacturer. Drug Safety. 2007; 30(8):715-726	Statistical methods – not topic of interest
Meyboom RHB, Royer RJ. Causality classification at pharmacovigilance centres in the european community. Pharmacoepidemiology and Drug Safety. 1992; 1(2):87-97	Causality terms only
Mull HJ, Nebeker JR. Informatics tools for the development of action-oriented triggers for outpatient adverse drug events. AMIA Annual Symposium Proceedings. 2008;505-509	Trigger tools – not topic of interest
Park MY, Yoon D, Lee K, Kang SY, Park I, Lee SH et al. A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database. Pharmacoepidemiology and Drug Safety. 2011; 20(6):598-607	ADR detection using extreme lab results – not algorithm
Patterson R, DeSwarte RD, Greenberger PA, Grammer LC, Brown JE, Choy AC. Drug allergy and protocols for management of drug allergies. Allergy Proceedings. 1994; 15(5):239-264	Protocols for in vitro testing – not topic of interest
Peyriere H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? British Journal of Dermatology. 2006; 155(2):422-428	No new algorithm
Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clinical Pharmacology and Therapeutics. 2010; 88(1):60-68	Does not address causality of drug reaction but focuses on comparisons between drugs that may cause a reaction
Schneider G, Kachroo S, Jones N, Crean S, Rotella P, Avetisyan R et al. A systematic review of validated methods for identifying hypersensitivity reactions other than anaphylaxis (fever, rash, and lymphadenopathy), using administrative	Addresses coding of algorithms. Does not address causality

Reference	Reason for exclusion
and claims data. Pharmacoepidemiology and Drug Safety. 2012; 21 Suppl 1:248-255	
Shah S, Shah H, Khaskheli MN, Akhtar J. Adverse drug reactions: clinical assessment of drug induced disease. Journal of Ayub Medical College, Abbottabad. 2005; 17(1):89-91	Narrative review
Smucker WD, Kontak JR. Adverse drug reactions causing hospital admission in an elderly population: experience with a decision algorithm. Journal of the American Board of Family Practice. 1990; 3(2):105-109	No new algorithm presented or already in systematic review
Spiegelhalter DJ. Computers, expert systems, and ADRs: Can causality assessment be automated? Drug Information Journal. 1986; 20(4):543-550	No new algorithm, description of possible computerised approach to ADR assessment
Steele JM. Diagnosis of the allergic state; a point scoring system. Annals of Allergy. 1956; 14(1):1-7	Not drug allergy
Strandell J, Caster O, Hopstadius J, Edwards IR, Noren GN. The development and evaluation of triage algorithms for early discovery of adverse drug interactions. Drug Safety: an International Journal of Medical Toxicology and Drug Experience. 2013; 36(5):371-388	Drug interaction rather than allergy
Stricker BHC. Diagnosis and causality assessment of drug-induced hepatic injury. In: Dukes MNG (eds), Drug-induced hepatic injury, Amsterdam: Elsevier, 1985: 1-13	Not drug allergy
Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Safety. 2002; 25(6):381-392	Data mining techniques, not topic of interest
Taft LM, Evans RS, Shyu CR, Egger MJ, Chawla N, Mitchell JA et al. Countering imbalanced datasets to improve adverse drug event predictive models in labor and delivery. Journal of Biomedical Informatics. 2009; 42(2):356-364	Statistical techniques
Tantikul C, Dhana N, Jongjarearnprasert K, Visitsunthorn N, Vichyanond P, Jirapongsananuruk O. The utility of the World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) system for the assessment of adverse drug reactions in hospitalized children. Asian Pacific Journal of Allergy and Immunology. 2008; 26(2-3):77-82	Global introspection – not primary care model
Tatonetti NP, Fernald GH, Altman RB. A novel signal detection algorithm for identifying hidden drug-drug interactions in adverse event reports. Journal of the American Medical Informatics Association. 2012; 19(1):79-85	Drug interactions, not drug allergy
Tatonetti NP, Denny JC, Altman RB. Response to 'use of an algorithm for identifying hidden drug-drug interactions in adverse event reports' by Gooden et al. Journal of the American Medical Informatics Association. 2013; 20(3):591	Correspondence
Theophile H, Arimone Y, Miremont-Salame G, Moore N, Fourrier-Reglat A, Haramburu F et al. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Safety. 2010; 33(11):1045-1054	No new algorithm presented or already in systematic review
Thyssen JP, Menne T, Elberling J, Plaschke P, Johansen JD. Hypersensitivity to local anaesthetics--update and proposal of evaluation algorithm. Contact Dermatitis. 2008; 59(2):69-78	Diagnostic treatment algorithm for testing of allergy
Tschepik W, Segal R, Sherrin TP, Schneider DN, Hammond RL. Therapeutic risk-assessment model for identifying patients with adverse drug reactions. American Journal of Hospital Pharmacy. 1990; 47(2):330-334	ADRS specific to theophylline and digoxin
Tuccori M, Giustarini G, Blandizzi C, Capogrosso-Sansone A, Rossi M, Gori G et al. Quality of adverse drug reaction (QADRA) reports: An algorithm to appraise the	Drug allergy not referred to

Reference	Reason for exclusion
efficiency of spontaneous reporting systems in pharmacovigilance. Journal of Public Health. 2013; 21(4):365-372	
Uyaniker M, Arikoglu T, Tufekci S, Kuyucu S. Evaluation of children admitted with a history of drug allergy: From claim to confirmation. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:381	Abstract only
Weiss J, Krebs S, Hoffmann C, Werner U, Neubert A, Brune K et al. Survey of adverse drug reactions on a pediatric ward: a strategy for early and detailed detection. Pediatrics. 2002; 110(2 Pt 1):254-257	No new algorithm – use of Naranjo algorithm
Wolfstadt JI, Gurwitz JH, Field TS, Lee M, Kalkar S, Wu W et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: a systematic review. Journal of General Internal Medicine. 2008; 23(4):451-458	See documentation rerun
Wongpoowarak W, Wongpoowarak P. Unified algorithm for real-time detection of drug interaction and drug allergy. Computer Methods and Programs in Biomedicine. 2002; 68(1):63-72	Does not address causality assessment but focuses on developing a database which identified possible cross-sensitivities
Yang L, Xu L, He L. A CitationRank algorithm inheriting Google technology designed to highlight genes responsible for serious adverse drug reaction. Bioinformatics. 2009; 25(17):2244-2250	Genetic testing – not topic of interest
Yoon D, Park MY, Choi NK, Park BJ, Kim JH, Park RW. Detection of adverse drug reaction signals using an electronic health records database: Comparison of the Laboratory Extreme Abnormality Ratio (CLEAR) algorithm. Clinical Pharmacology and Therapeutics. 2012; 91(3):467-474	Statistical methoths – not topic of interest
Zaki SA. Adverse drug reaction and causality assessment scales. Lung India. 2011; 28(2):152-153	Not new algorithm – use of Naranjo algorithm

K.2 Measuring serum tryptase after suspected anaphylaxis

Reference	Reason for exclusion
Assem ES. Predictive value of in vitro tests for the IgE-dependent and the IgE-independent anaphylactoid reactions to muscle relaxants. Annales Francaises D'Anesthesie Et De Reanimation. 1993; 12(2):203-211	No diagnostic accuracy; information on timing is for 1 patient. Excluded from Anaphylaxis guideline
Blanca M, Romano A, Torres MJ, Demoly P, DeWeck A. Continued need of appropriate betalactam-derived skin test reagents for the management of allergy to betalactams. Clinical and Experimental Allergy. 2007; 37(2):166-173	Narrative review
Bleasel KE, Donnan G, Unglik GA. General anesthetic allergy testing. Current Allergy and Asthma Reports. 2009; 9(1):50-56	Literature review
Borer-Reinhold M, Haeberli G, Bitzenhofer M, Jandus P, Hausmann O, Fricker M et al. An increase in serum tryptase even below 11.4ng/mL may indicate a mast cell-mediated hypersensitivity reaction: a prospective study in Hymenoptera venom allergic patients. Clinical and Experimental Allergy. 2011; 41(12):1777-1783	Not drug allergy patients
Chin Y, Williams A, Eren E, Walls A. Pre-and post-test blood samples to identify acutely raised serum tryptase levels contribute little additional information in the interpretation of drug allergy testing and food challenges. Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67:530-531	Conference abstract – no need to include since fully published studies are already included in the review
Dinakar C. Anaphylaxis in children: Current understanding and key issues in	Literature review

Reference	Reason for exclusion
diagnosis and treatment. Current Allergy and Asthma Reports. 2012; 12(6):641-649	
Dua S, Ewan PW. Tryptase measurement in 111 patients with suspected anaphylaxis during general anaesthesia. Clinical and Experimental Allergy. 2013; 42:1840	Unpublished (05/02/14)
Edston E, van Hage-Hamsten M. beta-Tryptase measurements post-mortem in anaphylactic deaths and in controls. Forensic Science International. 1998; 93(2-3):135-142	Post mortem measurements
Edston E, Eriksson O, Van Hage M. Mast cell tryptase in postmortem serum-reference values and confounders. International Journal of Legal Medicine. 2007; 121(4):275-280	Post mortem measurements
Enander I, Matsson P, Nystrand J, Andersson A-S, Eklund E, Bradford TR et al. A new radioimmunoassay for human mast cell tryptase using monoclonal antibodies. Journal of Immunological Methods. 1991; 138(1):39-46	Not a diagnostic study
Enrique E, Garcia-Ortega P, Sotorra O, Gaig P, Richart C. Usefulness of UniCAP-Tryptase fluoroimmunoassay in the diagnosis of anaphylaxis. Allergy. 1999; 54(6):602-606	Mixed population
Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. British Journal of Anaesthesia. 1998; 80(1):26-29	No clinical assessment. Excluded from anaphylaxis guideline.
Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: Postmortem findings and associated comorbid diseases. Annals of Allergy, Asthma and Immunology. 2007; 98(3):252-257	Case series. Not diagnostic testing
Gueant JL, Aimone-Gastin I, Namour F, Laroche D, Bellou A, Laxenaire MC. Diagnosis and pathogenesis of the anaphylactic and anaphylactoid reactions to anaesthetics. Clinical and Experimental Allergy. 1998; 28 Suppl 4:65-70	Review used as background
Harper NJN, Dixon T, Dugue, Edgar DM, Fay A, Gooi HC et al. Guidelines suspected anaphylactic reactions associated with anaesthesia. Anaesthesia. 2009; 64(2):199-211	Guideline
Kanthawatana S, Carias K, Arnaout R, Hu J, Irani AM, Schwartz LB. The potential clinical utility of serum alpha-protryptase levels. Journal of Allergy and Clinical Immunology. 1999; 103(6):1092-1099	Not question of interest
Komericki P, Arbab E, Grims R, Kranke B, Aberer W. Tryptase as severity marker in drug provocation tests. International Archives of Allergy and Immunology. 2006; 140(2):164-169	Not target population (mild allergic or non-allergic reactions)
Laroche D, Lefrancois C, Gerard J-L, Dubois F, Vergnaud M-C, Gueant J-L et al. Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs. British Journal of Anaesthesia. 1992; 69(6):611-614	Case series. Suxamethonium not reported separately
Laroche D, Namour F, Lefrancois C, Aimone-Gastin I, Romano A, Sainte-Laudy J et al. Anaphylactoid and anaphylactic reactions to iodinated contrast material. Allergy. 1999; 54 Suppl 58:13-16	Narrative review
Laroche D, Vergnaud MC, Dubois F, Bricard H. Plasma histamine and tryptase during anaphylactoid reactions. Agents and Actions. 1992; 36(SPEC. ISS.):C201-C202	Not drug allergy patients
Laxenaire MC, Mertes PM, Groupe d'Etudes des Reactions Anaphylactoides Peranesthesiques. Anaphylaxis during anaesthesia. Results of a two-year survey in France. British Journal of Anaesthesia. 2001; 87(4):549-558	Survey data
Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. Pathology. 2006; 38(4):328-332	Survey data
Mayer DE, Krauskopf A, Hemmer W, Moritz K, Jarisch R, Reiter C. Usefulness of post mortem determination of serum tryptase, histamine and diamine oxidase	Case series not drug allergy

Reference	Reason for exclusion
in the diagnosis of fatal anaphylaxis. Forensic Science International. 2011; 212(1-3):96-101	
McNeill O, Kerridge RK, Boyle MJ. Review of procedures for investigation of anaesthesia-associated anaphylaxis in Newcastle, Australia. Anaesthesia and Intensive Care. 2008; 36(2):201-207	Case series; not diagnostic testing
Michalska-Krzanowska G. Tryptase in diagnosing adverse suspected anaphylactic reaction. Advances in Clinical and Experimental Medicine. 2012; 21(3):403-408	Narrative review
Moreno F, Blanca M, Fernandez J, Ferrer A, Mayorga C, del Cano A et al. Determination of inflammatory markers in allergic reactions to drugs. Allergy and Asthma Proceedings. 1995; 16(3):119-122	No gold standard comparator
O'Brien RM, Pokorny CS. Investigating a patient with anaphylaxis. Medicine Today. 2006; 7(10):14-2	Not trial or diagnostic study
Ordoqui E, Zubeldia JM, Aranzabal A, Rubio M, Herrero T, Tornero P et al. Serum tryptase levels in adverse drug reactions. Allergy. 1997; 52(11):1102-1105	Case series; mixed population
Primeau MN, Adkinson NFJ. Recent advances in the diagnosis of drug allergy. Current Opinion in Allergy and Clinical Immunology. 2001; 1(4):337-341	Narrative review
Renz CL, Laroche D, Thurn JD, Finn HA, Lynch JP, Thisted R et al. Tryptase levels are not increased during vancomycin-induced anaphylactoid reactions. Anesthesiology. 1998; 89(3):620-625	No diagnostic accuracy or timing
Roberts ISD, Pumphrey RSH. Diagnosing anaphylaxis at autopsy. CPD Bulletin Cellular Pathology. 2001; 3(3):136-138	Narrative review
Romano A, Torres MJ, Castells M, Sanz ML, Blanca M. Diagnosis and management of drug hypersensitivity reactions. Journal of Allergy and Clinical Immunology. 2011; 127(3 Suppl):S67-S73	Narrative review
Schwartz LB, Bradford TR, Rouse C, Irani A-M, Rasp G, van der Zwan JK et al. Development of a new, more sensitive immunoassay for human tryptase: Use in systemic anaphylaxis. Journal of Clinical Immunology. 1994; 14(3):190-204	Not drug allergy patients
Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. Hematology/Oncology Clinics of North America. 2000; 14(3):641-657	Narrative review
Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunology and Allergy Clinics of North America. 2006; 26(3):451-463	Narrative review
Siles RI, Hsieh FH. Allergy blood testing: A practical guide for clinicians. Cleveland Clinic Journal of Medicine. 2011; 78(9):585-592	Narrative review
Simons FE. Anaphylaxis: Recent advances in assessment and treatment. Journal of Allergy and Clinical Immunology. 2009; 124(4):625-628	Narrative review
Simons FE. Anaphylaxis. Journal of Allergy and Clinical Immunology. 2010; 125(2 Suppl 2):S161-S181	Narrative review
Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SGA, Emergency Department. Elevated serum cytokines during human anaphylaxis: Identification of potential mediators of acute allergic reactions. Journal of Allergy and Clinical Immunology. 2009; 124(4):786	Not drug allergy
York MJ, Khan N. Local compliance to BSACI guidelines for the measurement of mast cell tryptase levels following suspected anaphylaxis to general anaesthetic agents. Clinical and Experimental Allergy. 2012; 42(12):1838	Conference abstract – no need to include since fully published studies are already included in the review

K.3 Measuring serum specific IgE

Reference	Reason for exclusion
Anania A. Measurement of specific IgEs in the diagnosis of drug allergy. Panminerva Medica. 1999; 41(2):115-117	No gold standard comparison
Antunez C, Blanca-Lopez N, Torres MJ, Mayorga C, Perez-Inestrosa E, Montanez MI et al. Immediate allergic reactions to cephalosporins: evaluation of cross-reactivity with a panel of penicillins and cephalosporins. Journal of Allergy and Clinical Immunology. 2006; 117(2):404-410	
Baldo BA. Diagnosis of allergy to penicillins and cephalosporins. Allergy and Clinical Immunology International. 2000; 12(5):206-212	Not question of interest
Blanca M, Mayorga C, Sanchez F, Vega JM, Fernandez J, Juarez C et al. Differences in serum IgE antibody activity to benzylpenicillin and amoxicillin measured by RAST in a group of penicillin allergic patients. Allergy. 1991; 46(8):632-638	Not question of interest
Charpin D, Benzarti M, Hemon Y, Senft M, Alazia M, Arnaud A et al. Atopy and anaphylactic reactions to suxamethonium. Journal of Allergy and Clinical Immunology. 1988; 82(3 Pt 1):356-360	No serum specific IgE done
Dona I, Blanca-Lopez N, Cornejo-Garcia JA, Torres MJ, Laguna JJ, Fernandez J et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clinical and Experimental Allergy. 2011; 41(1):86-95	Not question of interest
Fischer M, Roffe DJ. Allergy, atopy and IgE. The predictive value of total IgE and allergic history in anaphylactic reactions during anaesthesia. Anaesthesia. 1984; 39(3):213-217	No serum specific IgE done
Florvaag E, Johansson SGO, Oman H, Harboe T, Nopp A. Pholcodine stimulates a dramatic increase of IgE in IgE-sensitized individuals. A pilot study. Allergy. 2006; 61(1):49-55	Not question of interest
Garcia N, I, Barasona Villarejo MJ, Algaba Marmol MA, Moreno AC, Guerra PF. Diagnosis of patients with immediate hypersensitivity to s-Lactams using retest. Journal of Investigational Allergology and Clinical Immunology. 2012; 22(1):41-47	CAP results not provided
Fisher MM, Baldo BA. Mast cell tryptase in anaesthetic anaphylactoid reactions. British Journal of Anaesthesia. 1998; 80(1):26-29	No clinical assessment. Excluded from anaphylaxis guideline.
Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. Journal of Allergy and Clinical Immunology. 1992; 90(2):153-159	Not question of interest: comparison of in vitro tests
Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. Journal of Allergy and Clinical Immunology. 1992; 90(2):153-159	Not question of interest: histamine tests
Hamilton RG, MacGlashan J, Saini SS. IgE antibody-specific activity in human allergic disease. Immunologic Research. 2010; 47(1-3):273-284	Not drug allergy
Harboe T, Johansson SGO, Florvaag E, Oman H. Pholcodine exposure raises serum IgE in patients with previous anaphylaxis to neuromuscular blocking agents. Allergy. 2007; 62(12):1445-1450	Not question of interest
Harle DG, Baldo BA, Smal MA, Wajon P, Fisher MM. Detection of thiopentone-reactive IgE antibodies following anaphylactoid reactions during anaesthesia. Clinical Allergy. 1986; 16(5):493-498	Case series
Juhlin L, Ahlstedt S, Andal L, Ekstrom B, Svard PO, Wide L. Antibody reactivity in penicillin-sensitive patients determinated with different penicillin derivatives.	Case series

Reference	Reason for exclusion
International Archives of Allergy and Applied Immunology. 1977; 54(1):19-28	
Lafuente A, Javaloyes G, Berroa F, Goikoetxea MJ, Moncada R, Nunez-Cordoba JM et al. Early skin testing is effective for diagnosis of hypersensitivity reactions occurring during anesthesia. Allergy. 2013; 68(6):820-822	Focus on skin tests, IgE results not clearly described
Laurent LJ, Parish HJ. Unreliability of local reactions to serum as tests for general sensitivity. British Journal of Preventive and Social Medicine. 1962; 16:111-112	Editorial
Layton GT, Stanworth DR, Amos HE. The incidence of IgE and IgG antibodies to chlorhexidine. Clinical and Experimental Allergy. 1989; 19(3):307-314	Not all participants tested against gold standard
Lazarenko L. Detection of IgE- and IgG-antibodies to local anaesthetics and dental materials. What is the diagnostic value? Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67(S96):128	Conference abstract – no need to include since fully published studies are already included in the review
Mayorga C, Sanz ML, Gamboa PM, Garcia BE, Caballero MT, Garcia JM et al. In vitro diagnosis of immediate allergic reactions to drugs: an update. Journal of Investigational Allergology and Clinical Immunology. 2010; 20(2):103-109	Narrative review
Montanez M, Ruiz-Sanchez A, Ariza A, Mayorga C, Perez-Inestrosa E, Rodriguez-Bada J et al. Dual haptenic presentation in carrier molecules for the in vitro testing to detect IgE-antibodies in patients allergic to betalactams. Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67(6):127-128	Conference abstract – no need to include since fully published studies are already included in the review
Moreno F, Blanca M, Mayorga C, Terrados S, Moya M, Perez E et al. Studies of the specificities of IgE antibodies found in sera from subjects with allergic reactions to penicillins. International Archives of Allergy and Immunology. 1995; 108(1):74-81	No gold standard
Palma-Carlos ML, Palma-Carlos AG, Medina M. "In vivo" and "in vitro" tests in the diagnosis of Beta-lactams allergy. European Annals of Allergy and Clinical Immunology. 2007; 39(5):157-161	Data extraction not possible
Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. Journal of Pediatrics. 1998; 132(1):137-143	Comparison to clinical symptoms
Richter AG, Nasser SM, Krishna MT. A UK national survey of investigations for beta-lactam hypersensitivity - heterogeneity in practice and a need for national guidelines - on behalf of British Society for Allergy and Clinical Immunology (BSACI). Clinical and Experimental Allergy. 2013; 43(8 6):941-949	IgE results not clearly described
Romano A, Gaeta F, Valluzzi RL, Alonzi C, Viola M, Bousquet PJ. Diagnosing hypersensitivity reactions to cephalosporins in children. Pediatrics. 2008; 122(3):521-527	Case series
Romano A, Gaeta F, Valluzzi RL, Caruso C, Rumi G, Bousquet PJ. IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability of penicillins, monobactams, and carbapenems. Journal of Allergy and Clinical Immunology. 2010; 126(5):994-999	No question of interest
Sagar PS, Katelaris CH. Utility of penicillin allergy testing in patients presenting with a history of penicillin allergy. Asia Pacific Allergy. 2013; 3(2 6):115-119	Background reading
Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA. 2001; 285(19):2498-2505	Not question of interest
Sanz ML, Prieto I, Garcia BE, Oehling A. Diagnostic reliability considerations of specific IgE determination. Journal of Investigational Allergology and Clinical	Not question of interest

Reference	Reason for exclusion
Immunology. 1996; 6(3):152-161	
Schnyder B, Pichler WJ. Skin and laboratory tests in amoxicillin- and penicillin-induced morbilliform skin eruption. Clinical and Experimental Allergy. 2000; 30(4):590-595	Case series
Silva R, Cruz L, Botelho C, Castro E, Cadinha S, Castel-Branco MG et al. Immediate hypersensitivity to penicillins with negative skin tests - The value of specific IgE. European Annals of Allergy and Clinical Immunology. 2009; 41(4):117-119	Narrative review
Simons FER, Ardusso LRF, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF et al. World allergy organization anaphylaxis guidelines: 2013 update of the evidence base. International Archives of Allergy and Immunology. 2013; 162(3):193-204	Provides background information
Worrall GJ, Hull C, Briffett E. Radioallergosorbent testing for penicillin allergy in family practice. Canadian Medical Association Journal. 1994; 150(1):37-41	Not question of interest
Zhao Z, Baldo BA, Baumgart KW, Mallon DF. Fine structural recognition specificities of IgE antibodies distinguishing amoxicilloyl and amoxicillanyl determinants in allergic subjects. Journal of Molecular Recognition. 2001; 14(5):300-307	Case study
Zidarn M, Silar M, Vegnuti M, Korosec P, Kosnik M. The specificity of tests for anti-beta-lactam IgE antibodies declines progressively with increase of total serum IgE. Wiener Klinische Wochenschrift. 2009; 121(9-10):353-356	Not question of interest
Zhu DX, Zhao JL, Mo L, Li HL. Drug allergy: identification and characterization of IgE-reactivities to aspirin and related compounds. Journal of Investigational Allergology and Clinical Immunology. 1997; 7(3):160-168	Case series

K.4 Documenting and sharing information with other healthcare professionals

Reference	Reason for exclusion
CPOE: It's not a ... say the experts, so the time to prepare is now. ED Management. 2006; 18(1):1-3	Descriptive – no effectiveness data
New guidelines prevent costly adverse drug reactions. Healthcare Demand and Disease Management. 2000; 6(4):59-49	Summary of US guidance
Penicillin allergy and radioallergosorbent testing. Journal of the American Osteopathic Association. 1994; 94(2):120	Letter to the editor
Reduce anaphylactic reactions to anaesthetic drugs by identifying definite risk factors and preventing subsequent reactions. Drugs and Therapy Perspectives. 2005; 21(2):24-26	Prognostic study not related to documentation strategy
The disc that saves lives. Rehabilitation in South Africa. 1974; 18(4):114	Descriptive only – no data to extract
AbdulAzeez S, Al Tajir GK, Sulieman H. Assessment of the current practice of antibiotic skin testing in a tertiary hospital in United Arab Emirates. Journal of Infection in Developing Countries. 2011; 5(11):759-764	Not related to documentation strategies
Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: General considerations. Allergy. 2003; 58(9):854-863	Not related to documentation strategies
Abookire SA, Teich JM, Sandige H, Paterno MD, Martin MT, Kuperman GJ et al. Improving allergy alerting in a computerized physician order entry system. Proceedings AMIA Symposium. 2000;2-6	Descriptive data only – no efficacy outcomes
Absy M, Glatt AE. Antibiotic allergy: inaccurate history taking in a teaching hospital. Southern Medical Journal. 1994; 87(8):805-807	Not related to documentation strategies
Adams J, Adinaro D, Baumlin K, Aldeen A, Christensen M, Courtney DM et al.	Abstract of a design and

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Gedi wise: Geriatric emergency department innovations in care through workforce, informatics, and structural enhancements. Annals of Emergency Medicine. 2013; 62(4 SUPPL. 1):S54-S55	rationale paper
Alexander S, Forman L. Which of the drugs caused the rash? Or the value of the lymphocyte transformation test in eruptions caused by nalidixic acid. British Journal of Dermatology. 1971; 84(5):429-434	Not related to documentation strategies
Alldred DP, Standage C, Zermansky AG, Barber ND, Raynor DK, Petty DR. The recording of drug sensitivities for older people living in care homes. British Journal of Clinical Pharmacology. 2010; 69(5):553-557	Comparisons not relevant to the protocol question
Alldred DP, Raynor DK, Hughes C, Barber N, Chen TF, Spoor P. Interventions to optimise prescribing for older people in care homes. Cochrane Database of Systematic Reviews. 2013; Issue 2:CD009095	Drug allergies not separately reported
Allen PD, Fuentes RJ, Hoopes MJ, Susla G. Evaluation of Drug Adverse Event Intake and Reporting in a Medical Information Service. Drug Information Journal. 2011; 45(6):767-773	Description of a pharmaceutical industry based information system and how adverse events were being reported
Amin W, Hitch G, Molai S, Khan I, Mulla R. A clinical audit on reporting and documentation of penicillin allergy at an NHS Foundation Trust Hospital. International Journal of Pharmacy Practice. 2010; 18:36-37	Conference abstract
Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. Journal of the American Medical Informatics Association: JAMIA. 2008; 15(5):585-600	Systematic review – no mention of drug allergy errors (cross checked for references)
An S-Y, Hwang E-K, Kim J-H, Kim J-E, Jin H-J, Jin S-M et al. Vancomycin-associated spontaneous cutaneous adverse drug reactions. Allergy, Asthma and Immunology Research. 2011; 3(3):194-198	Not related to documentation strategies
Anderson J, Shroff D, Curtis A, Eldridge N, Cannon K, Karnani R et al. The Veterans Affairs shift change physician-to-physician handoff project. Joint Commission Journal on Quality and Patient Safety. 2010; 36(2):62-71	Outcomes not related to drug allergies
Anoz-Jimenez L, Ferrer-Ferrer C, Becerril-Moreno F, Navarro-de-Lara S, Estaun-Diaz-de-Villegas E. Nursing interventions as part of an integral pharmaceutical care team. Farmacia Hospitalaria. 2011; 35(1):1-7	Not in English
Apter AJ, Kinman JL, Bilker WB, Herlim M, Margolis DJ, Lautenbach E et al. Represcription of penicillin after allergic-like events. Journal of Allergy and Clinical Immunology. 2004; 113(4):764-770	Not related to documentation strategies
Armour CL. Penicillin allergy documentation and reliability in two Sydney teaching hospitals. Australian Journal of Hospital Pharmacy. 1998; 28(6):410-412	No intervention comparison
Arroliga ME, Wagner W, Bobek MB, Hoffman-Hogg L, Gordon SM, Arroliga AC. A pilot study of penicillin skin testing in patients with a history of penicillin allergy admitted to a medical ICU. Chest. 2000; 118(4):1106-1108	Not related to documentation strategies
Atanaskovic-Markovic M, Gaeta F, Medjo B, Viola M, Nestorovic B, Romano A. Tolerability of meropenem in children with IgE-mediated hypersensitivity to penicillins. Allergy. 2008; 63(2):237-240	Not related to documentation strategies
Au WY. Relevance of drug allergy history after allogeneic hemopoietic stem cell transplantation. Bone Marrow Transplantation. 2007; 40(2):179-180	Letter to the editor
Bale J. Allergic to penicillin: written in her notes and on an armband, but a doctor gave her the drug anyway and she died. 2006. [Last accessed: 28 February 2013]	Case study
Balon D, Stevens RG. Design of a computer program for automatic capture of adverse drug interaction and contraindication data detected during	Description of design features – no

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prescription labelling. International Journal of Pharmacy Practice. 1997; 5(2):105-110	effectiveness data
Baluga JC, Casamayou R, Carozzi E, Lopez N, Anale R, Borges R et al. Allergy to local anaesthetics in dentistry. Myth or reality? Allergologia Et Immunopathologia. 2002; 30(1):14-19	Not related to documentation strategies
Barnett J, Jennings H. Pharmacy information systems in Canada. Studies in Health Technology and Informatics. 2009; 143:131-135	Not related to documentation strategies
Bates DW. Frequency, consequences and prevention of adverse drug events. Journal of Quality in Clinical Practice. 1999; 19(1):13-17	Not related to documentation strategies
Beckwith MC, Najari Z, Hermes ER. Latex hypersensitivity. Journal of Pharmaceutical Care in Pain and Symptom Control. 1994; 2(3):25-36	Not related to documentation strategies
Beyea SC, Hicks RW. Oops--the patient is allergic to that medication. AORN Journal. 2003; 77(3):650-654	No effectiveness data
Bhandari S, Armitage J, Chintu M, Chinnappa S, Kendrew P. The use of pharmaceuticals for dialysis patients. How well do we know our patients' allergies? Journal of Renal Care. 2008; 34(4):213-217	Not related to documentation strategies
Bhattacharya S. The facts about penicillin allergy: A review. Journal of Advanced Pharmaceutical Technology and Research. 2010; 1(1):11-17	Not related to documentation strategies
Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of suspected and challenge-verified penicillin allergy in a university hospital population. Basic and Clinical Pharmacology and Toxicology. 2006; 98(4):357-362	Not related to documentation strategies
Brousseau G. Integrated clinical information system. Medinfo MEDINFO. 1995; 8 Pt 1:459	Descriptive – no effectiveness data
Brown EL, Raue PJ, Mlodzianowski AE, Meyers BS, Greenberg RL, Bruce ML. Transition to home care: quality of mental health, pharmacy, and medical history information. International Journal of Psychiatry in Medicine. 2006; 36(3):339-349	Not related to documentation strategies
Browne K. MedicAlert -- more than just a bracelet! Accident and Emergency Nursing. 2003; 11(4):239-242	Descriptive – no effectiveness data
Burda SA, Hobson D, Pronovost PJ. What is the patient really taking? Discrepancies between surgery and anesthesiology preoperative medication histories. Quality and Safety in Health Care. 2005; 14(6):414-416	Not related to documentation strategies
Burke CE, Piper J, Calderon J. Inconsistent documentation of drug-related allergies and adverse effects in patient charts. American Journal of Health-System Pharmacy. 1998; 55(3):289-290	Letter to the editor
Burrell C, Tsourounis C, Quan D, Jue V, Tam E, Guglielmo BJ. Impact of a pharmacist-driven protocol to improve drug allergy documentation at a university hospital. Hospital Pharmacy. 2013; 48(4):302-307	Pharmacist review
Cameron C, Maling T. Fatal allergic reactions to antibiotics. New Zealand Medical Journal. 2008; 121(1286):132-133	Case report
Campi P, Benucci M, Manfredi M, Demoly P. Hypersensitivity reactions to biological agents with special emphasis on tumor necrosis factor-alpha antagonists. Current Opinion in Allergy and Clinical Immunology. 2007; 7(5):393-403	Not related to documentation strategies
Celiker V, Basgul E, Karakaya G, Oguzalp H, Bozkurt B, Kalyoncu AF. General anesthesia and postoperative pain management in analgesic intolerant patients with/without astha: Is it safe? Allergologia Et Immunopathologia. 2004; 32(2):64-68	Not related to documentation strategies
Chaffee BW, Zimmerman CR. Developing and implementing clinical decision support for use in a computerized prescriber-order-entry system. American Journal of Health-System Pharmacy. 2010; 67(5):391-400	Descriptive – no effectiveness data

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Chalabianloo F, Berstad A, Schjott J, Riedel B, Irgens A, Florvaag E. Clinical characteristics of patients with drug hypersensitivity in Norway: a single-centre study. Pharmacoepidemiology and Drug Safety. 2011; 20(5):506-513	Not related to documentation strategies
Chamisa I, Zulu BMW. Setting the records straight - A prospective audit of the quality of case notes in a surgical department. South African Journal of Surgery. 2007; 45(3):92-95	Not related specifically to drug allergies
Chan KW. Medical records can be improved. Hong Kong Practitioner. 2002; 24(5):228-231	Descriptive – no effectiveness data
Chase PA, Bainbridge J. Care plan for documenting pharmacist activities. American Journal of Hospital Pharmacy. 1993; 50(9):1885-1888	Not related to documentation strategies for drug allergies
Chazard E, Ficheur G, Merlin B, Serrot E, PSIP consortium, Beuscart R. Adverse drug events prevention rules: multi-site evaluation of rules from various sources. Studies in Health Technology and Informatics. 2009; 148:102-111	Descriptive only – no data to extract
Cheam H, Butani L. Immunoglobulin E-mediated reactions to corticosteroids. Current Allergy and Asthma Reports. 2005; 5(1):22-27	Not related to documentation strategies
Cheong EA, Katelaris CH, Sisson CM, Anderson EA, Byth K. Adverse drug reactions associated with home parenteral therapy. Journal of Pharmacy Practice and Research. 2008; 38(4):267-270	Not related to documentation strategies
Christian S, Gyves H, Manji M. Electronic prescribing. Care of the Critically Ill. 2004; 20(3):68-71	Non-systematic review
Chronaki CE, Chiarugi F. Interoperability as a quality label for portable & wearable health monitoring systems. Studies in Health Technology and Informatics. 2005; 117:108-116	Descriptive – no effectiveness data
Cohen MR. Look in and on the patient's chart for allergy information. Nursing. 1985; 15(4):14	Case report
Collins DJ, Nickless GD, Green CF. Medication histories: Does anyone know what medicines a patient should be taking? International Journal of Pharmacy Practice. 2004; 12(4):173-178	Pharmacist review
Confino-Cohen R, Leader A, Klein N, Pereg D, Khoury S, Perl L et al. Drug allergy in hospitalized patients: the contribution of allergy consultation and a structured questionnaire. International Archives of Allergy and Immunology. 2012; 158(3):307-312	Related to accuracy rather than documentation strategy.
Coombes ID, Reid C, McDougall D, Stowasser D, Duiguid M, Mitchell C. Pilot of a National Inpatient Medication Chart in Australia: improving prescribing safety and enabling prescribing training. British Journal of Clinical Pharmacology. 2011; 72(2):338-349	Drug allergy errors not separately analysed
Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the National Reporting and Learning System in England and Wales over 6 years (2005-2010). British Journal of Clinical Pharmacology. 2012; 74(4):597-604	An updated version included in the introduction
Cresswell KM, Sheikh A. Lessons from the UK National Patient Safety Agency's National Reporting and Learning System on reducing drug allergies. Primary Care Respiratory Journal. 2008; 17(1):3-4	Editorial
Cresswell KM, Sheikh A. Information technology-based approaches to reducing repeat drug exposure in patients with known drug allergies. Journal of Allergy and Clinical Immunology. 2008; 121(5):1112-1117	Review – cross checked for references
Dantonio C, Galimberti M, Barbone B, Calamari M, Airoldi G, Campanini M et al. Suspected acute allergic reactions: analysis of admissions to the Emergency Department of the AOU Maggiore della Carita Hospital in Novara from 2003 to 2007. European Annals of Allergy and Clinical Immunology. 2008; 40(4):122-129	Not related to documentation strategies

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Dartnell JGA, Crowe DM, Schubert AL, Moulds RFW. Review of the use of adverse drug reaction labels on medical records. Australian Journal of Hospital Pharmacy. 1994; 24(4):333-335	No intervention comparison
Daulat S, Solensky R, Earl HS, Casey W, Gruchalla RS. Safety of cephalosporin administration to patients with histories of penicillin allergy. Journal of Allergy and Clinical Immunology. 2004; 113(6):1220-1222	Not related to documentation strategies
Davis CP. Emergency department visits: we are not prepared. American Journal of Emergency Medicine. 2012; 30(8):1364-1370	Not related to documentation strategies
DeLeo JM, Pucino F, Calis KA, Crawford KW, Dorworth T, Gallelli JF. Patient-interactive computer system for obtaining medication histories. American Journal of Hospital Pharmacy. 1993; 50(11):2348-2352	Patient experience with regard to drug allergies were not described
Delgado-Jimenez Y, Perez-Gala S, Aragues M, Sanchez-Perez J, Garcia-Diez A. Late skin reaction to iodixanol (Visipaque): clinical manifestations, patch test study, and histopathological evaluation. Contact Dermatitis. 2006; 55(6):348-353	Not related to documentation strategies
Demoly P. Anaphylactic reactions - Value of skin and provocation tests. Toxicology. 2005; 209(2):221-223	Allergy testing rather than documentation
DeMoor PA, Matusov Y, Kelly C, Kolan S, Barnachea L, Bazhenova LA. A retrospective review of the frequency and nature of acute hypersensitivity reactions at a medium-sized infusion center: Comparison to reported values and inconsistencies found in literature. Journal of Cancer. 2011; 2(1):153-164	Not related to documentation strategies
Deshmukh AA, Sommerville H. Survey of the needs of patients in a private nursing home: A pharmacist's view. International Journal of Pharmacy Practice. 1996; 4(2):83-87	Not related to documentation strategies
Dilles T, Vander Stichele RH, Van Bortel LM, Elseviers MM. The development and test of an intervention to improve ADR screening in nursing homes. Journal of the American Medical Directors Association. 2013; 14(5):379-6	No outcomes related to allergy
Doherty K, Segal A, McKinney PG. The 10 most common prescribing errors: Tips on avoiding the pitfalls. Consultant. 2004; 44(2):173-182	Hints and tips article – no effectiveness data
Drain KL, Volcheck GW. Preventing and managing drug-induced anaphylaxis. Drug Safety. 2001; 24(11):843-853	Not related to documentation strategies
Eggleston ST, Lush LW. Understanding allergic reactions to local anesthetics. Annals of Pharmacotherapy. 1996; 30(7-8):851-857	Not related to documentation strategies
Epstein N. Adverse and allergic reactions to drugs. Canadian Family Physician Medecin De Famille Canadien. 1975; 21(11):67-70	Not related to documentation strategies
Evans RS, Pestotnik SL, Classen DC, Bass SB, Burke JP. Prevention of adverse drug events through computerized surveillance. Proceedingsof the Annual Symposium on Computer Application in Medical Care. 1992;437-441	Results reported in full in an included study by the same authors
Ewan PW, Dugue P, Mirakian R, Dixon TA, Harper JN, Nasser SM et al. BSACI guidelines for the investigation of suspected anaphylaxis during general anaesthesia. Clinical and Experimental Allergy. 2010; 40(1):15-31	Background reading
Fabbian F, Melandri R, Borsetti G, Micaglio E, Pala M, De GA et al. Color-coding triage and allergic reactions in an Italian ED. American Journal of Emergency Medicine. 2012; 30(5):826-829	Descriptive – no effectiveness data
Ferner RE, Coleman JJ. An algorithm for integrating contraindications into electronic prescribing decision support. Drug Safety. 2010; 33(12):1089-1096	Descriptive – no effectiveness data
Fink III JL. Liability when dispensing to allergic patients. Pharmacy Times. 2008; 74(9):54	Not related to documentation strategies
Fisher M, Rose MA. Follow-up of patients after testing for anaesthetic allergy. Anaesthesia and Intensive Care. 2011; 39(6):1160	Not related to communication strategies
Fisher MM, Roffe DJ. Allergy, atopy and IgE. The predictive value of total IgE	Not related to

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and allergic history in anaphylactic reactions during anaesthesia. Anaesthesia. 1984; 39(3):213-217	documentation strategies
Fisher MM, Jones K, Rose M. Follow-up after anaesthetic anaphylaxis. Acta Anaesthesiologica Scandinavica. 2011; 55(1):99-103	Correspondence
Fitzgerald RJ. Medication errors: the importance of an accurate drug history. British Journal of Clinical Pharmacology. 2009; 67(6):671-675	Descriptive – no effectiveness data
Fitzsimons M, Grimes T, Galvin M. Sources of pre-admission medication information: observational study of accuracy and availability. International Journal of Pharmacy Practice. 2011; 19(6):408-416	Related to accuracy rather than documentation strategy
Foisy MM, Tseng A. Development of an interactive computer-assisted program to manage medication therapy in HIV infected patients. Drug Information Journal. 1998; 32(3):649-656	Descriptive – no effectiveness data
Fonacier L, Hirschberg R, Gerson S. Adverse drug reactions to a cephalosporins in hospitalized patients with a history of penicillin allergy. Allergy and Asthma Proceedings. 2005; 26(2):135-141	Not related to documentation strategies
Forni A, Chu HT, Fanikos J. Technology utilization to prevent medication errors. Current Drug Safety. 2010; 5(1):13-18	Review – background reading
Frank G, Lawless ST, Steinberg TH. Improving physician communication through an automated, integrated sign-out system. Journal of Healthcare Information Management. 2005; 19(4):68-74	Descriptive – no effectiveness data
Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? Annals of Pharmacotherapy. 2009; 43(2):304-315	Not related to documentation strategies
Fung KW, Vogel LH. Will decision support in medications order entry save money? A return on investment analysis of the case of the Hong Kong hospital authority. AMIA Annual Symposium Proceedings. 2003;244-248	Related to costs of computer system
Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E et al. Adverse drug events in ambulatory care. New England Journal of Medicine. 2003; 348(16):1556-1564	Adverse drug reactions rather than allergies – only 1 event described as drug allergy
Gay KJ, Hill C, Bell T. Accuracy of drug-allergy recording in a district general hospital. International Journal of Pharmacy Practice. 2009; 17(4):253-255	Not related to documentation strategies
Ghibelli S, Marengoni A, Djade CD, Nobili A, Tettamanti M, Franchi C et al. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck()). Drugs and Aging. 2013; 30(10):821-828	The objective of the study and the purpose of the intervention was to stop inappropriate medications in older adults, and not related to allergies
Glenn WL, Patry RA, Kroeger R. Pharmacy services in a Federal extended care facility, as provided by a pharmacy student. Journal of the American Geriatrics Society. 1978; 26(7):331-334	Pharmacist review – case study
Glover R, Trottier L. Pharmacy involvement in the evaluation of drug allergies. Canadian Journal of Hospital Pharmacy. 1977; 30(2):38-44	Pharmacist review
Gonzalez-Gregori R, Dolores Hernandez Fernandez De Rojas, Lopez-Salgueiro R, Diaz-Palacios M, Garcia AN. Allergy alerts in electronic health records for hospitalized patients. Annals of Allergy, Asthma and Immunology. 2012; 109(2):137-140	Descriptive – no effectiveness data
Gouveia WA. Managing pharmacy information systems. American Journal of Hospital Pharmacy. 1993; 50(1):113-116	Descriptive – no effectiveness data
Gowan J, Roller L. Allergy and adverse drug reaction - Skin rashes and itching. Australian Journal of Pharmacy. 2008; 89(1061):63-67	Review – not related to documentation strategies

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Green CR, Mottram DR, Pirmohamed M, Horner R, Rowe PH. Communication regarding adverse drug reactions between secondary and primary care: A postal questionnaire survey of general practitioners. Journal of Clinical Pharmacy and Therapeutics. 1999; 24(2):133-139	Outcomes not relevant to drug allergies
Greenberger PA, Patterson R, Fotis MA. Penicillin allergy: improving patient care and the medical record. Allergy and Asthma Proceedings. 2000; 21(5):295-296	Editorial
Hammann F, Gutmann H, Vogt N, Helma C, Drewe J. Prediction of adverse drug reactions using decision tree modeling. Clinical Pharmacology and Therapeutics. 2010; 88(1):52-59	Economic paper
Hannaford PC. Adverse drug reaction cards carried by patients. BMJ. 1986; 292(6528):1109-1112	Descriptive – no effectiveness data
Hansen NL, Chandiramani DV, Morse MA, Wei D, Hedrick NE, Hansen RA. Incidence and predictors of cetuximab hypersensitivity reactions in a North Carolina academic medical center. Journal of Oncology Pharmacy Practice. 2011; 17(2):125-130	Not related to documentation strategies
Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clinical Pharmacology and Therapeutics. 2013; 93(6):539-546	Not relevant to documentation
Hatton K, McKenzie CA, Barrett NA. Improving allergy documentation. 2011. [Last accessed: 14 March 2012]	Comment
Hoffmann RP, Ellerbrock MC, Lovett JE. A multihospital medication allergy audit: A means to quality assurance. Hospital Pharmacy. 1982; 17(4):202-211	Not related to documentation strategies
Holzman TG, Griffith A, Hunter WG, Allen T, Simpson J. Computer-assisted trauma care prototype. Medinfo MEDINFO. 1995; 8 Pt 2:1685	Not related to drug allergy documentation
Horsky J, Schiff GD, Johnston D, Mercincavage L, Bell D, Middleton B. Interface design principles for usable decision support: A targeted review of best practices for clinical prescribing interventions. Journal of Biomedical Informatics. 2012; 45(6):1202-1216	General review – background reading
Hulse RK, Clark SJ, Jackson JC, Warner HR, Gardner RM. Computerized medication monitoring system. American Journal of Hospital Pharmacy. 1976; 33(10):1061-1064	Descriptive – no effectiveness data
Hume AL, Quilliam BJ, Goldman R, Eaton C, Lapane KL. Alternatives to potentially inappropriate medications for use in e-prescribing software: triggers and treatment algorithms. BMJ Quality and Safety. 2011; 20(10):875-884	The intervention does not match the protocol.
Husband AK, Lloyd C, Worsley AJ, Skelly DM. An audit of drug allergy documentation in a district hospital. International Journal of Pharmacy Practice. 2007; 15(S2):B73-B74	Descriptive – no effectiveness data
Hussein O, Zaidise I, Linn S. Safety and cost of computerized physician order entry in Internal Medicine Department. European Journal of Internal Medicine. 2013; 24:e268-e269	Conference abstract: evidence from fully published studies sufficiently available
Iedema R, Ball C, Daly B, Young J, Green T, Middleton PM et al. Design and trial of a new ambulance-to-emergency department handover protocol: 'IMIST-AMBO'. BMJ Quality and Safety. 2012; 21(8):627-633	Not related to documentation strategies specific to drug allergies
Irmiter C, Subbarao I, Shah JN, Sokol P, James JJ. Personal derived health information: a foundation to preparing the United States for disasters and public health emergencies. Disaster Medicine and Public Health Preparedness. 2012; 6(3):303-310	Unobtainable
Isaac T, Weissman JS, Davis RB, Massagli M, Cyrulik A, Sands DZ et al. Overrides	Factors predicting alert

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of medication alerts in ambulatory care. Archives of Internal Medicine. 2009; 169(3):305-311	acceptance rather than documentation strategy
Ismail ZF, Ismail TF, Wilson AJ. Improving safety for patients with allergies: An intervention for improving allergy documentation. Clinical Governance. 2008; 13(2):86-94	Pharmacy review
Jabbour AA, Briceland LL, Lomaestro BM, Timm EG. Allergy documentation in patients prescribed vancomycin: The role of the pharmacist. Journal of Infectious Disease Pharmacotherapy. 2002; 5(4):21-32	Pharmacist review
Jani YH, Barber N, Wong ICK. Characteristics of clinical decision support alert overrides in an electronic prescribing system at a tertiary care paediatric hospital. International Journal of Pharmacy Practice. 2011; 19(5):363-366	Descriptive – no effectiveness data
Jayawardena S, Eisdorfer J, Indulkar S, Pal SA, Sooriabalan D, Cucco R. Prescription errors and the impact of computerized prescription order entry system in a community-based hospital. American Journal of Therapeutics. 2007; 14(4):336-340	Comparisons not relevant
Johnson V, Croft C, Crane V. Counseling patients about drug allergies in the inpatient setting. American Journal of Health-System Pharmacy. 2001; 58(19):1855-1858	Not related to documentation strategies
Johnston CA, Mole AB. Patient care computer in 68-bed hospital. Journal of the American Medical Record Association. 1980; 51(4):28-36	Not related to documentation strategies
Johnstone DM, Kirking DM, Vinson BE. Comparison of adverse drug reactions detected by pharmacy and medical records departments. American Journal of Health-System Pharmacy. 1995; 52(3):297-301	Unobtainable
Jones EW. Summary care records in urgent and emergency care in England. Acute Medicine. 2013; 12(3):178-180	Introduction, description and discussion of an intervention and does not look at its effects or compare with other interventions
Jones TA, Como JA. Assessment of medication errors that involved drug allergies at a university hospital. Pharmacotherapy. 2003; 23(7):855-860	Descriptive data only
Jose RJ, Sinha-Ray R, Fiandeiro PT, Boateng L, Ali FR. An audit of in-patients' allergy status documentation at a large inner-city teaching hospital NHS Trust. Clinical and Experimental Allergy. 2012; 42(12):1830	Conference abstract describing current practice.
Kaelber DC, Bates DW. Health information exchange and patient safety. Journal of Biomedical Informatics. 2007; 40(6 Suppl):S40-S45	Descriptive – no effectiveness data
Kalliat R, Smith N, Graham-Clarke E, Kong KL. An audit of the completeness and accuracy of allergy-status documentation. Clinical Pharmacist. 2010; 2:369	Descriptive – no effectiveness data
Kaluarachchi SI, Fernandopulle BMR, Gunawardane BP. Hepatic and haematological adverse reactions associated with the use of multidrug therapy in leprosy - A five year retrospective study. Indian Journal of Leprosy. 2001; 73(2):121-129	Not related to documentation strategies
Kamboj S, Yousef E, McGeady S, Hossain J. The prevalence of antibiotic skin test reactivity in a pediatric population. Allergy and Asthma Proceedings. 2011; 32(2):99-105	Not related to documentation strategies
Kaushal R, Kern LM, Barron Y, Quaresimo J, Abramson EL. Electronic prescribing improves medication safety in community-based office practices. Journal of General Internal Medicine. 2010; 25(6):530-536	Subset of the population of an already included study (Abramson et al, 2011)
Khalil H, Leversha A, Khalil V. Drug allergy documentation--time for a change? International Journal of Clinical Pharmacy. 2011; 33(4):610-613	Comment paper

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Kilbridge PM, Campbell UC, Cozart HB, Mojarrad MG. Automated surveillance for adverse drug events at a community hospital and an academic medical center. Journal of the American Medical Informatics Association. 2006; 13(4):372-377	Process evaluation: early stage implementation of ADE surveillance
Kilbridge PM, Noirot LA, Reichley RM, Berchelmann KM, Schneider C, Heard KM et al. Computerized surveillance for adverse drug events in a pediatric hospital. Journal of the American Medical Informatics Association. 2009; 16(5):607-612	Process evaluation: description of surveillance implementation and its evaluation
Kloet MA, Smithburger PL, Seybert AL, Kane-Gill SL. Assessment of inpatient boxed warning compliance. Pharmacotherapy. 2012; 32(10):e219	Conference abstract on prescriber compliance to a form of documentation
Kluger N, Aldasouqi S. A new purpose for tattoos: Medical alert tattoos. Presse Medicale. 2013; 42(2):134-137	Descriptive – no effectiveness data
Kraemer MJ, Caprye-Boos H, Berman HS. Increased use of medical services and antibiotics by children who claim a prior penicillin sensitivity. Western Journal of Medicine. 1987; 146(6):697-700	Not related to documentation strategy
Krau SD, McInnis LA, Parsons L. Allergy Skin Testing: What Nurses Need to Know. Critical Care Nursing Clinics of North America. 2010; 22(1):75-82	Related to training rather than documentation strategy
Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? British Journal of Anaesthesia. 2005; 95(4):468-471	Not related to documentation strategy
Kuehm SL, Doyle MJ. Medication errors: 1977 to 1988. Experience in medical malpractice claims. New Jersey Medicine. 1990; 87(1):27-34	Not related to documentation strategies
Kuperman GJ, Marston E, Paterno M, Rogala J, Plaks N, Hanson C et al. Creating an enterprise-wide allergy repository at Partners HealthCare System. AMIA Annual Symposium Proceedings. 2003;376-380	Descriptive – no effectiveness data
Lager S, White B, Baumann M, Mitchem RE, Jackson R, Black N. Incidence of cross-sensitivity with carbapenems in documented penicillin-allergic patients. Journal of Pharmacy Technology. 2009; 25(3):159-163	Restricted to cross-sensitivity and not related to documentation strategy
Lainer M, Mann E, Sonnichsen A. Information technology interventions to improve medication safety in primary care: a systematic review. International Journal for Quality in Health Care. 2013; 25(5):590-598	Systematic review with focus on IT intervention to reduce medication errors but no reference to allergies
Langley JM, Halperin S. Allergy to antibiotics in children: Perception versus reality. Canadian Journal of Infectious Diseases. 2002; 13(3):160-163	Not related to documentation strategies
Lawton K, Skjoet P. Assessment of three systems to empower the patient and decrease the risk of adverse drug events. Studies in Health Technology and Informatics. 2011; 166:246-253	Descriptive – no effectiveness data
Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. Pediatrics. 2006; 118(2):555-562	Not related to documentation strategies
Leape LL, Kabcenell AI, Gandhi TK, Carver P, Nolan TW, Berwick DM. Reducing adverse drug events: lessons from a breakthrough series collaborative. Joint Commission Journal on Quality Improvement. 2000; 26(6):321-331	Description of proposed changes
Lee AG, Anderson R, Kardon RH, Wall M. Presumed "sulfa allergy" in patients with intracranial hypertension treated with acetazolamide or furosemide: cross-reactivity, myth or reality? American Journal of Ophthalmology. 2004; 138(1):114-118	Not related to documentation strategies
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Liccardi G, Lobefalo G, Di Florio E, Di Iorio C, Occhiochiuso L, Romano L et al. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. Journal of Investigational Allergology and Clinical Immunology. 2008; 18(1):1-11	Not related to documentation strategies
Lopez R, Gonzalez R, Hernandez D, Hervas D, Campos A, Diaz M et al. Allergy alerts in hospital electronic medical records. Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67:108	Conference abstract describing use of allergy alert entries and patients' allergy profile but with no comparison
Lubowski TJ, Cronin LM, Pavelka RW, Briscoe-Dwyer LA, Briceland LL, Hamilton RA. Effectiveness of a medication reconciliation project conducted by PharmD students. American Journal of Pharmaceutical Education. 2007; 71(5)	Medication reconciliation
Luque I, Leyva L, Jose Torres M, Rosal M, Mayorga C, Segura JM et al. In vitro T-cell responses to beta-lactam drugs in immediate and nonimmediate allergic reactions. Allergy. 2001; 56(7):611-618	Not related to documentation strategies
Mabry ME, Miller RA. Distinguishing drug toxicity syndromes from medical diseases: A QMR computer-based approach. Computer Methods and Programs in Biomedicine. 1991; 35(4):301-310	Not related to documentation strategies
Mackowiak LR, Hayward SL. Issues of decision support in institutional pharmacy systems. Pharmacy Practice Management Quarterly. 1998; 18(1):35-45	Review – no effectiveness data
MacPherson RD, Willcox C, Chow C, Wang A. Anaesthetist's responses to patients' self-reported drug allergies. British Journal of Anaesthesia. 2006; 97(5):634-639	Not related to documentation strategies
Macy E, Mangat R, Burchette RJ. Penicillin skin testing in advance of need: Multiyear follow-up in 568 test result-negative subjects exposed to oral penicillins. Journal of Allergy and Clinical Immunology. 2003; 111(5):1111-1115	Not related to documentation strategies
Madaan A, Li JTC. Cephalosporin allergy. Immunology and Allergy Clinics of North America. 2004; 24(3):463-476	Not related to documentation strategies
Marsden D, Libretto SE. Hypersensitivity to topiramate sprinkle capsules does not preclude the use of topiramate tablets. Pediatric Drugs. 2004; 6(2):133-135	Not related to documentation strategies
Marvin V, Woodfield G, Kuo S, Donnellan S, Bovill I. Pilot study of the use of a medicaton review tool as an aid to stopping unnecessary medicines in older hospital patients. Pharmacoepidemiology and Drug Safety. 2013; 22(6):682-683	Conference abstract with incomplete data of a pilot study
Matthew R, Mary H, Franklin BD. Documentation of medication-related hospital admissions. Pharmacoepidemiology and Drug Safety. 2013; 22(6):687-688	Conference abstract that describes current practice
Mawby J. Accurate documenting of a patient's drug allergy status will promote informed therapy decision-making. Pharmacy in Practice. 2006; 16(1):24-25	Research letter
McCall C, Maynes B, Zou CC, Zhang NJ. An automatic medication self-management and monitoring system for independently living patients. Medical Engineering and Physics. 2013; 35(4):505-514	The focus is on development of an intervention rather than its effectiveness
McCallum AD, Duncan CJA, MacDonald R, Jones ME. A decade of vaccinating allergic travellers: A clinical audit. Travel Medicine and Infectious Disease. 2011; 9(5):231-237	Not related to documentation strategies

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McClimon B, Rank M, Li J. The predictive value of skin testing in the diagnosis of local anesthetic allergy. Allergy and Asthma Proceedings. 2011; 32(2):95-98	Not related to documentation strategies
McConnell SA, Penzak SR, Warmack TS, Anaissie EJ, Gubbins PO. Incidence of imipenem hypersensitivity reactions in febrile neutropenic bone marrow transplant patients with a history of penicillin allergy. Clinical Infectious Diseases. 2000; 31(6):1512-1514	Not related to documentation strategies
McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Annals of Pharmacotherapy. 2002; 36(9):1331-1336	Not related to documentation strategies
McKenzie CA, Hatton K, Barrett NA. Improving the accuracy and timeliness of medication allergy documentation in the intensive care unit. Pharmaceutical Journal. 2011; 287:578	Descriptive – no effectiveness data
McLernon DJ, Bond CM, Lee AJ, Watson MC, Hannaford PC, Fortnum H et al. Patient views and experiences of making adverse drug reaction reports to the Yellow Card Scheme in the UK. Pharmacoepidemiology and Drug Safety. 2011; 20(5):523-531	Adverse drug reactions – drug allergies not mentioned
McMurry M, Thomas E, Irons R, Seifert C. Identification of inappropriate prescribing in elderly patients admitted and discharged from a community hospital using the stopp screening tool. Consultant Pharmacist. 2012; 27(10):703	Abstract of poster which focused on identification of current practice
McRobbie D, Bednall R, West T. Assessing the impact of re-engineering of pharmacy services to general medical wards. Pharmaceutical Journal. 2003; 270(7239):342-345	Not related to documentation strategies
Mendelson LM. Adverse reactions to beta-lactam antibiotics. Immunology and Allergy Clinics of North America. 1998; 18(4):745-757	Review – not related to documentation
Menduno M. Software that plays hardball. Expert clinical systems fend off forgetfulness, mistakes, and fraud investigators. Hospitals and Health Networks. 1998; 72(10):44-48	Descriptive – no effectiveness data
Mertes PM, Laxenaire M-C. Anaphylaxis during general anaesthesia: Prevention and management. CNS Drugs. 2000; 14(2):115-133	Not related to drug allergy documentation
Michael PA. Physician-directed software design: the role of utilization statistics and user input in enhancing HELP results review capabilities. Proceedings / the Annual Symposium on Computer Application [Sic] in Medical Care Symposium on Computer Applications in Medical Care. 1993;107-111	Descriptive – no effectiveness data
Michael PA. ROUNDS: a customizable HELP results review program for hospital staff physicians. Proceedings / the Annual Symposium on Computer Application [Sic] in Medical Care Symposium on Computer Applications in Medical Care. 1992;327-331	Descriptive – no effectiveness data
Mills DH. Allergic reactions to drugs. A survey on hospital practices of soliciting medical information from newly admitted patients. California Medicine. 1964; 101:4-8	Not relevant to current practice
Moore P, Armitage G, Wright J, Dobrzanski S, Ansari N, Hammond I et al. Medicines reconciliation using a shared electronic health care record. Journal of Patient Safety. 2011; 7(3):148-154	Medicine reconciliation
Moreno S, Mestres C, Ponce A, Bertran J. Implementation of different strategies to improve the detection of drug adverse reactions. International Journal of Clinical Pharmacy. 2013; 35(5 SUPPL. 2):929	Conference abstract: evidence from fully published studies sufficiently available
Morritt AN, Alexander DJ. Impact of junior doctor education on drug allergy documentation. Annals of the Royal College of Surgeons of England. 2005; 87(4):311-312	Letter to the editor
Moss J, Saidman LJ. Are histamine-releasing drugs really contraindicated in patients with a known allergy to drugs? [7]. Anesthesiology. 1993; 79(3):623-	Correspondence

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Moss RB, Babin S, Hsu YP, Blessing-Moore J, Lewiston NJ. Allergy to semisynthetic penicillins in cystic fibrosis. Journal of Pediatrics. 1984; 104(3):460-466	Not related to documentation strategies
Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. Journal of Allergy and Clinical Immunology. 1991; 87(1 Pt 1):78-88	Not related to documentation strategies
Murphy J, Daly P. Using evidence-based knowledge in a nursing documentation system. Studies in Health Technology and Informatics. 2006; 122:1003	No study data
Mysore V, Nischal KC. Guidelines for administration of local anesthesia for dermatosurgery and cosmetic dermatology procedures. Indian Journal of Dermatology, Venereology and Leprology. 2009; 75(SUPPL. 2):S68-S75	Not related to documentation strategies
Nadarajah K, Green GR, Naglak M. Clinical outcomes of penicillin skin testing. Annals of Allergy, Asthma and Immunology. 2005; 95(6):541-545	Not related to documentation strategies
Nicole G. Decreasing inappropriate prescribing in elderly patients Regina. Pharmacotherapy. 2012; 32(10):e182	Conference abstract with focus on prescription of high severity medications in elderly patients
Noren GN, Edwards IR. Modern methods of pharmacovigilance: Detecting adverse effects of drugs. Clinical Medicine, Journal of the Royal College of Physicians of London. 2009; 9(5):486-489	Narrative review
Nudelman PM, Madsen SA. GHC's innovative pharmacy system. Hospital Materiel Management Quarterly. 1982; 4(1):1-10	Unobtainable
Nurenberg JR, Schleifer SJ. Reported allergies to antipsychotic agents in a long-term psychiatric hospital. Journal of Psychiatric Practice. 2009; 15(6):489-492	Allergies to antipsychotics – not related to documentation strategies
Oborne CA, Hooper R, Swift CG, Jackson SHD. Explicit, evidence-based criteria to assess the quality of prescribing to elderly nursing home residents. Age and Ageing. 2003; 32(1):102-108	Editorial
Oswald NT. Penicillin allergy: a suspect label. BMJ. 1983; 287(6387):265-266	Not related to documentation strategies
Ottaiano A, Tambaro R, Greggi S, Prato R, Di Maio M, Esposito G et al. Safety of cisplatin after severe hypersensitivity reactions to carboplatin in patients with recurrent ovarian carcinoma. Anticancer Research. 2003; 23(4):3465-3468	Not related to documentation strategies
Pablo AJ, Castells M. Drug allergy in pediatric patients. Pediatric Annals. 2011; 40(4):200-204	Not related to documentation strategies
Park MA, McClimon BJ, Ferguson B, Markus PJ, Odell L, Swanson A et al. Collaboration between allergists and pharmacists increases -lactam antibiotic prescriptions in patients with a history of penicillin allergy. International Archives of Allergy and Immunology. 2011; 154(1):57-62	Documentation strategy not described
Parmar JS, Nasser S. Antibiotic allergy in cystic fibrosis. Thorax. 2005; 60(6):517-520	Not related to documentation strategies
Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. Journal of Allergy and Clinical Immunology. 2012; 129(2):443-447	Not related to documentation strategies
Pau AK, Morgan JE, Terlingo A. Drug allergy documentation by physicians, nurses, and medical students. American Journal of Hospital Pharmacy. 1989; 46(3):570-573	Comparison not relevant
Paul L, Robinson KM. Capture and documentation of coded data on adverse drug reactions: an overview. HIM Journal. 2012; 41(3):27-36	Descriptive – no effectiveness data
Payne TH, Nichol WP, Hoey P, Savarino J. Characteristics and override rates of	Descriptive – no

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order checks in a practitioner order entry system. Proceedings / AMIA Annual Symposium AMIA Symposium. 2002;602-606	effectiveness data
Pearson TF, Pittman DG, Longley JM, Grapes ZT, Vigliotti DJ, Mullis SR. Factors associated with preventable adverse drug reactions. American Journal of Hospital Pharmacy. 1994; 51(18):2268-2272	Not related to documentation strategies
Pelaez LM, Gelber SE, Fox NS, Chasen ST. Inappropriate use of vancomycin for preventing perinatal group B streptococcal (GBS) disease in laboring patients. Journal of Perinatal Medicine. 2009; 37(5):487-489	Not related to documentation strategies
Peterson H. A health care system in Sweden. Journal of Clinical Computing. 1982; 11(4):136-163	Descriptive – no effectiveness data
Pleasants RA, Kessler JM. Drug allergies, adverse drug reactions, and the patient record [2]. American Journal of Hospital Pharmacy. 1993; 50(7):1363	Letter to the editor
Ponegalek B. Development of a hospital-based patient summary record. Disease Management. 1999; 2(4):115-118	Descriptive – no effectiveness data
Prescott WAJ, DePestel DD, Ellis JJ, Regal RE. Incidence of carbapenem-associated allergic-type reactions among patients with versus patients without a reported penicillin allergy. Clinical Infectious Diseases. 2004; 38(8):1102-1107	Not related to documentation strategies
Preston SL, Briceland LL, Lesar TS. Accuracy of penicillin allergy reporting. American Journal of Hospital Pharmacy. 1994; 51(1):79-84	Focus on accuracy rather than communication strategy
Pronovost P, Weast B, Schwarz M, Wyskiel RM, Prow D, Milanovich SN et al. Medication reconciliation: a practical tool to reduce the risk of medication errors. Journal of Critical Care. 2003; 18(4):201-205	Medication reconciliation
Przybilla B, Aberer W, Bircher AJ, Brehler R, Brockow K, Dickel H et al. Allergological approach to drug hypersensitivity reactions. JDDG - Journal of the German Society of Dermatology. 2008; 6(3):240-243	Not related to documentation strategies
Quinn H. Inaccurate documentation of drug allergy status results from gaps in staff knowledge. Pharmacy in Practice. 2003; 13(9):308-310	Descriptive data only
Rabi SM, Dahdal WY. Implementation of a pharmacist resident medication reconciliation program. Pharmacy Education. 2007; 7(4):351-357	Pharmacist review – reconciliation
Radford A, Undre S, Alkhamesi NA, Darzi SA. Recording of drug allergies: are we doing enough? Journal of Evaluation in Clinical Practice. 2007; 13(1):130-137	Descriptive data only
Rahmner PB, Eiermann B, Korkmaz S, Gustafsson LL, Gruven M, Maxwell S et al. Physicians' reported needs of drug information at point of care in Sweden. British Journal of Clinical Pharmacology. 2012; 73(1):115-125	Focus group discussions and questionnaire on the needs of physicians
Randolph TC, Parker A, Meyer L, Zeina R. Effect of a pharmacist-managed culture review process on antimicrobial therapy in an emergency department. American Journal of Health-System Pharmacy. 2011; 68(10):916-919	Pharmacist review
Renaut C. Audit of a local allergy policy shows deficits in recording allergy status. Pharmacy in Practice. 2005; 15(4):153-157	Not related to documentation strategies
Rimawi RH, Shah KB, Cook PP. Risk of redocumenting penicillin allergy in a cohort of patients with negative penicillin skin tests. Journal of Hospital Medicine. 2013; 8(11):615-618	Assessment of risk of redocumentation of allergy rather than an assessment of impact of a documentation strategy
Roberts DS, Mahoney EJ, Hutchinson CT, Aliphas A, Grundfast KM. Analysis of recurrent angiotensin converting enzyme inhibitor-induced angioedema. Laryngoscope. 2008; 118(12):2115-2120	Not related to documentation strategies
Romano A, Viola M, Gueant-Rodriguez RM, Gaeta F, Valluzzi R, Gueant JL. Brief communication: tolerability of meropenem in patients with IgE-mediated	Not related to documentation strategies

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Romano A, Gueant-Rodriguez RM, Viola M, Pettinato R, Gueant JL. Cross-reactivity and tolerability of cephalosporins in patients with immediate hypersensitivity to penicillins. Annals of Internal Medicine. 2004; 141(1):16-22	Not related to documentation strategies
Rommers MK, Zwaveling J, Guchelaar HJ, Teepe-Twiss IM. Evaluation of rule effectiveness and positive predictive value of clinical rules in a Dutch clinical decision support system in daily hospital pharmacy practice. Artificial Intelligence in Medicine. 2013; 59(1):15-21	The onus is on the hospital pharmacists
Rosenwasser R, Winterstein AG, Rosenberg AF, Rosenberg EI, Antonelli PJ. Perioperative medication errors in otolaryngology. Laryngoscope. 2010; 120(6):1214-1219	Descriptive data only
Runciman WB, Roughead EE, Semple SJ, Adams RJ. Adverse drug events and medication errors in Australia. International Journal for Quality in Health Care. 2003; 15 Suppl 1:i49-i59	Not related to documentation strategies
Russell WJ. Cross-Reactivity Documented for Hemaccel and Gelofusin. Anesthesia and Analgesia. 2004; 98(5):1499	Letter to the editor
Sandager T. Medication and problem list. Quality Letter for Healthcare Leaders. 1999; 11(3):26-27	Not a study
Sanz ML, Gamboa PM, Antepara I, Uasuf C, Vila L, Garcia-Aviles C et al. Flow cytometric basophil activation test by detection of CD63 expression in patients with immediate-type reactions to betalactam antibiotics. Clinical and Experimental Allergy. 2002; 32(2):277-286	Not related to documentation strategies
Sarrasin JJ, Schumacher M, Hay C, Richard P. Health-Identity: mobile services for consumers of medicines. Studies in Health Technology and Informatics. 2010; 155:153-159	Descriptive – no effectiveness data
Saxon A, Macy E, Endres HG, Wetstone HJ, Strom BL, Schinnar R et al. Cross-Reactivity and Sulfonamide Antibiotics(multiple letters). New England Journal of Medicine. 2004; 350(3):302-303	Correspondence
Sim L, Barras M, Cottrell N. Patients' understanding of drug allergy and documentation - Is there a link? Journal of Pharmacy Practice and Research. 2005; 35(4):276-278	Not related to documentation strategies specific to drug allergies.
Sittig DF. Personal health records on the internet: A snapshot of the pioneers at the end of the 20th Century. International Journal of Medical Informatics. 2002; 65(1):1-6	Descriptive – no effectiveness data
Slight SP, Nanji KC, Seger DL, Cho I, Volk LA, Bates DW. Overrides of clinical decision support alerts in primary care clinics. Studies in Health Technology and Informatics. 2013; 192:923	No intervention comparison
Smith M, Dang D, Lee J. E-prescribing: clinical implications for patients with diabetes. Journal of Diabetes Science and Technology. 2009; 3(5):1215-1218	Descriptive – no effectiveness data
Smith RG. Penicillin and cephalosporin drug allergies: a paradigm shift. Journal of the American Podiatric Medical Association. 2008; 98(6):479-488	Not related to documentation strategies
Snyder RA, Abarca J, Meza JL, Rothschild JM, Rizos A, Bates DW. Reliability evaluation of the adapted national coordinating council medication error reporting and prevention (NCC MERP) index. Pharmacoepidemiology and Drug Safety. 2007; 16(9):1006-1013	Description and evaluation of a set of criteria used for CPOE
Sohel J, Clark BS, Paton C. Allergies and adverse drug reactions: clinical records versus patients' perceptions. Journal of Mental Health. 2009; 18(1):51-56	Not related to documentation strategies
Soller RW, Shaheen C, Yen J, Rose J, Lightwood J. Erratum to Improvement of the Drug Allergy Alert for Nonprescription NSAIDs (Drug Information Journal, 46, 3 (336-343), 10.1177/0092861512440951). Drug Information Journal. 2012;	Erratum related to an included study – error not relevant to the extracted

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46(5):627	information
Stair TO. Reduction of redundant laboratory orders by access to computerized patient records. Journal of Emergency Medicine. 1998; 16(6):895-897	Non comparative study
Steinberg P. Anaphylaxis: 36 Commonsense ways to reduce the risk. Consultant. 2009; 49(8)	Not related to documentation strategies
Stember RH. Prevalence of skin test reactivity in patients with convincing, vague, and unacceptable histories of penicillin allergy. Allergy and Asthma Proceedings. 2005; 26(1):59-64	Not related to documentation strategies
Stephens M, Fox B, Kukulka G, Bellamy J. Medication, allergy, and adverse drug event discrepancies in ambulatory care. Family Medicine. 2008; 40(2):107-110	Not related to documentation strategies
Steven ID, Malpass A, Moller J, Runciman WB, Helps SC. Towards safer drug use in general practice. Journal of Quality in Clinical Practice. 1999; 19(1):47-50	Not related to documentation strategies
Stock R, Scott J, Gurtel S. Using an electronic prescribing system to ensure accurate medication lists in a large multidisciplinary medical group. Joint Commission Journal on Quality and Patient Safety. 2009; 35(5):271-277	Medicine reconciliation
Sullivan KM, Spooner LM. Adverse-drug-reaction reporting by pharmacy students in a teaching hospital. American Journal of Health-System Pharmacy. 2008; 65(12):1177-1179	Pharmacist review
Tamayo E, Alvarez FJ, Castrodeza J, Yanez J, Arnaiz P, Lajo C et al. Self-reported drug allergies and the diagnostic work-up in the surgical population. Journal of Evaluation in Clinical Practice. 2010; 16(5):902-904	Prevalence of self-reported allergies rather than documentation of it
Tamblyn R. Improving patient safety through computerized drug management: the devil is in the details. HealthcarePapers. 2004; 5(3):52-84	Descriptive – no effectiveness data
Tamblyn RM, Jacques A, Laprise R, Huang A, Perreault R. The Office of the Future Project: the integration of new technology into office practice. Academic detailing through the super highway. Quebec Research Group on Medication Use in the Elderly. Clinical Performance and Quality Health Care. 1997; 5(2):104-108	Descriptive – no effectiveness data
Tan LE, Lee AS. Hospital based drug allergy register in Singapore. Annals of the Academy of Medicine, Singapore. 1990; 19(5):666-671	Descriptive – no effectiveness data
Tate J, Mein J, Freeman H, Maguire G. Grey nomads--health and health preparation of older travellers in remote Australia. Australian Family Physician. 2006; 35(1-2):70-72	Not related to documentation strategies
Taylor LK, Kawasumi Y, Bartlett G, Tamblyn R. Inappropriate prescribing practices: the challenge and opportunity for patient safety. Healthcare Quarterly. 2005; 8 Spec No:81-85	Descriptive – no effectiveness data
Tempest A. Auditing the recording of allergy status in community hospitals. Hospital Pharmacist. 2006; 13(7):259-260	Background information
Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Safety. 2004; 27(11):819-829	Not related to documentation strategies
Thien FCK. 3. Drug hypersensitivity. Medical Journal of Australia. 2006; 185(6):333-338	Not related to documentation strategies
Thienthong S, Hintong T, Pulnitiporn A. The Thai Anesthesia Incidents Study (THAI Study) of perioperative allergic reactions. Journal of the Medical Association of Thailand. 2005; 88(SUPPL. 7):S128-S133	Unobtainable
Thomson PJ, Fletcher IR, Downey C. Nurses versus clinicians - Who's best at pre-operative assessment? Ambulatory Surgery. 2004; 11(1-2):33-36	Not related to documentation strategies
Thurmann PA. Prescribing errors resulting in adverse drug events: How can they be prevented? Expert Opinion on Drug Safety. 2006; 5(4):489-493	Review- background reading

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Torres MJ, Mayorga C, Leyva L, Guzman AE, Cornejo-Garcia JA, Juarez C et al. Controlled administration of penicillin to patients with a positive history but negative skin and specific serum IgE tests. Clinical and Experimental Allergy. 2002; 32(2):270-276	Not related to drug allergy documentation
Trinkle R. Gender differences among patients reporting medication allergies. Journal of Pharmacy Technology. 1999; 15(3):90-93	Not related to drug allergy documentation
Tripp DM, Brown GR. Pharmacist assessment of drug allergies. American Journal of Hospital Pharmacy. 1993; 50(1):95-98	Pharmacist review
Turner RD. Are we aware of hospital patients' drug allergies? Journal of Clinical Pharmacy and Therapeutics. 2006; 31(6):649-650	Letter to the editor
Valente S, Murray LP. Creative strategies to improve patient safety: allergies and adverse drug reactions. Journal for Nurses in Staff Development. 2011; 27(1):E1-E7	Descriptive – no effectiveness data
Valente S, Murray L, Fisher D. Nurses improve medication safety with medication allergy and adverse drug reports. Journal of Nursing Care Quality. 2007; 22(4):322-327	Related to staff training rather than documentation strategy
van den Bemt PM, van den Broek S, van Nunen AK, Harbers JB, Lenderink AW. Medication reconciliation performed by pharmacy technicians at the time of preoperative screening. Annals of Pharmacotherapy. 2009; 43(5):868-874	Medication reconciliation
van der Linden CMJ, Jansen PAF, Grouls RJE, van Marum RJ, Verberne MAJW, Aussems LMA et al. Systems that prevent unwanted represcription of drugs withdrawn because of adverse drug events: A systematic review. Therapeutic Advances in Drug Safety. 2013; 4(2):73-90	Review – cross checked for references
van Walraven C, Weinberg AL. Quality assessment of a discharge summary system. CMAJ. 1995; 152(9):1437-1442	Descriptive study – no effectiveness data
Ved P, Coupe T. Improving prescription quality in an in-patient mental health unit: Three cycles of clinical audit. Psychiatric Bulletin. 2007; 31(8):293-294	Not related to documentation strategies
Vilensky D, MacDonald RD. Communication errors in dispatch of air medical transport. Prehospital Emergency Care. 2011; 15(1):39-43	Not related to communication strategies
Villamanan E, Larrubia Y, Ruano M, Herrero A, Alvarez-Sala R. Strategies for improving documentation and reducing medication errors related to drug allergy. International Journal of Clinical Pharmacy. 2011; 33(6):879-880	Letter to the editor
Wang M, Lau C, Matsen FA, Kim Y. Personal health information management system and its application in referral management. IEEE Transactions on Information Technology in Biomedicine. 2004; 8(3):287-297	Outcomes not related to drug allergies
Ward L, Innes M. Electronic medical summaries in general practice - Considering the patient's contribution. British Journal of General Practice. 2003; 53(489):293-297	Not aimed to explore issues related to drug allergies
Warnekar PP, Bouhaddou O, Parrish F, Do N, Kilbourne J, Brown SH et al. Use of RxNorm to exchange codified drug allergy information between Department of Veterans Affairs (VA) and Department of Defense (DoD). AMIA Annual Symposium Proceedings. 2007;781-785	Computer system design – no effectiveness data
Weiss ME, Adkinson NF, Jr. Diagnostic testing for drug hypersensitivity. Immunology and Allergy Clinics of North America. 1998; 18(4):731-744	Review – not focused on documentation
West SL, D'Aloisio AA, Ringel-Kulka T, Waller AE, Clayton Bordley W. Population-based drug-related anaphylaxis in children and adolescents captured by South Carolina Emergency Room Hospital Discharge Database (SCERHDD) (2000-2002). Pharmacoepidemiology and Drug Safety. 2007; 16(12):1255-1267	Not related to communication strategies
Wickern GM, Nish WA, Bitner AS, Freeman TM. Allergy to beta-lactams: a survey of current practices. Journal of Allergy and Clinical Immunology. 1994;	Not related to documentation strategies

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94(4):725-731	
Wilcock M, Harding G, Moore L, Nicholls I, Powell N, Stratton J. What do hospital staff in the UK think are the causes of penicillin medication errors? International Journal of Clinical Pharmacy. 2013; 35(1):72-78	Not related to documentation strategies
Wiwanitkit V. Repeated prescription of known identified drugs with a history of drug allergy. Journal of Pharmacology and Pharmacotherapeutics. 2011; 2(2):133-134	Letter to the editor
Wohrl S, Vigl K, Stingl G. Patients with drug reactions -- is it worth testing? Allergy. 2006; 61(8):928-934	Not related to documentation strategies
Wyer SL. Documentation of penicillin allergy in a Veterans' Hospital. Australian Journal of Hospital Pharmacy. 1997; 27(4):296-301	Descriptive data only
Yourman L, Concato J, Agostini JV. Use of computer decision support interventions to improve medication prescribing in older adults: A systematic review. American Journal Geriatric Pharmacotherapy. 2008; 6(2):119-129	Review which sought for studies with variable outcome measures not pertinent to the protocol
Yusuff KB, Tayo F, Aina BA. Pharmacists' participation in the documentation of medication history in a developing setting: An exploratory assessment with new criteria. Pharmacy Practice. 2010; 8(2):139-145	Pharmacy review
Zanotti K, Kulp B, Peterson G, Markman M. Relationship between a history of systemic allergic reactions and risk of subsequent carboplatin hypersensitivity. Gynecologic Oncology. 2003; 89(3):514-516	Not related to documentation strategies
Zimmerman CR, Chaffee BW, Lazarou J, Gingrich CA, Russell CL, Galbraith M et al. Maintaining the enterprisewide continuity and interoperability of patient allergy data. American Journal of Health-System Pharmacy. 2009; 66(7):671-679	Descriptive – no data to extract

K.5 Providing information and support to patients

Reference	Reason for exclusion
National Council on Patient Information and Education advises consumers "wait, educate, before you self-medicate". School Nurse News. 2008; 25(4):13-15	Summary article
Aagaard L, Christensen A, Hansen EH. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. British Journal of Clinical Pharmacology. 2010; 70(4):481-491	No relevant information; only drug class and prevalence of ADR in children
Abelson MB, Hom MM. Improved patient questionnaires ease allergy diagnosis, enable targeted therapy ABELSON2006. Ocular Surgery News. 2006; 24(6):40	Opinion review
Alkhawajah AM, Eferakeya AE. The role of pharmacists in patients' education on medication. Public Health. 1992; 106(3):231-237	No relevant information: only role of pharmacist in medication information
Baiardini I, Puggioni F, Menoni S, Boot J, Diamant Z, Braido F et al. Patient knowledge, perceptions, expectations, and satisfaction, on subcutaneous and sublingual allergenspecific immunotherapy: A real life survey. Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67:337-338	Conference abstract
Bailey SC, Schillinger D, Chen A, Sarkar U, Larsen E, Wolf M. Factors associated with adverse drug events among non-English speaking patients. Journal of General Internal Medicine. 2011; 26:S352	Abstract
Baniasadi S, Fahimi F, Namdar R. Development of an adverse drug reaction bulletin in a teaching hospital. Formulary. 2009; 44(11):333-335	No relevant information: description of an ADR

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Barnett CW. Need for community pharmacist-provided food-allergy education and auto-injectable epinephrine training. Journal of the American Pharmacists Association. 2005; 45(4):479-485	No relevant information: survey of confidence in recognising allergic reaction to food and use of EpiPen
Bennett H, Gajewski M, Shah G, Byrnes P, Kramer D, Sebaoun T. Preferences of high and low anxiety patients in avoiding common anesthetic outcomes. Anesthesia and Analgesia. 2011; 112(5 SUPPL. 1)	Abstract – not relevant
Berry DC, Michas IC, Gillie T, Forster M. What do patients want to know about their medicines, and what do doctors want to tell them: a comparative study. Psychology & Health. 1997; 12(4):467-480	Study focused on adverse drug reactions. Drug allergies not explicitly referred to
Blalock SJ, Patel RA. Drug therapy concerns questionnaire: initial development and refinement. Journal of the American Pharmacists Association. 2005; 45(2):160-169	Development of scale
Borres MP, Brakenhielm G, Irander K. How many teenagers think they have allergic rhinoconjunctivitis and what they do about it. Annals of Allergy, Asthma and Immunology. 1997; 78(1):29-34	Survey of perception – not related to drug allergy
Bourgeois FT, Mandl KD, Valim C, Shannon MW. Pediatric adverse drug events in the outpatient setting: an 11-year national analysis. Pediatrics. 2009; 124(4):e744-e750	Statistics of ADR by medication class and system affected
Bowrey DJ, Morris-Stiff GJ. Drug allergy: fact or fiction? International Journal of Clinical Practice. 1998; 52(1):20-21	Addresses categorisation of drug allergy probability
Brouneus F, Macleod G, Maclennan K, Parkin L, Paul C. Drug safety awareness in New Zealand: public knowledge and preferred sources for information. Journal of Primary Health Care. 2012; 4(4):288-293	Not specific for drug allergy. Survey of general knowledge about medication
Burton C, Irshad T, Sheikh A. Understanding the experiences of allergy testing: a qualitative study of people with perceived serious allergic disorders. Postgraduate Medical Journal. 2010; 86(1020):591-596	Experience of anaphylaxis
Butt TF, Cox A, Lewis H, Ferner R. Experiences of survivors of drug-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and their attitudes to medications and adverse drug reactions. British Journal of Clinical Pharmacology. 2010; 70(2):290	Abstract – full paper included
Canoves L, Ballester E, Ortega E, Abril V, Deltoro MG. Anxiety, depression, adverse events and cognitive Therapy. HIV Medicine. 2009; 10:121	Abstract
Chee B, Berlin R, Schatz B. Measuring population health using personal health messages. AMIA Annual Symposium Proceedings / AMIA Symposium AMIA Symposium. 2009; 2009:92-96	No information about drug allergy
Cheema E, Singer D, Sakr M, Watkins J, Bal K. Poor knowledge about medicines is linked to increased history of adverse drug reactions among patients attending the emergency department with acute medical problems. International Journal of Pharmacy Practice. 2012; 20:26-27	Abstract only
Chivato T, De BF, Bousquet J, Cardona V, Demoly P, Fontana L et al. Understanding treatment of patients in allergic diseases (UTOPIA program). Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:145	Abstract – describes a continuous medical education programme
Clyne B, Hughes C, Smith SM, Fahey T. Feasibility of medicines review to reduce potentially inappropriate medicines in the elderly: The opti-script cluster randomized controlled trial. Value in Health. 2013; 16(7):A485	No reference to drug allergies
Costello M, Taylor S, Hourihane JOB, DunnGalvin A. Impact of hazard control over risk assessment on the allergic consumer: A FARRP study. Journal of Allergy and Clinical Immunology. 2011; 127(2 SUPPL. 1):AB118	Food allergy – abstract only

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Cowan JD, Burns D, Palmer TW, Scott J, Feeback E. A palliative medicine program in a community setting: 12 Points from the first 12 months. American Journal of Hospice and Palliative Medicine. 2003; 20(6):415-433	No relevant information
Dever SI, Polmear-Swendris N, McMorris M, Baptist A. An educational intervention can improve quality of life in food allergic families. Journal of Allergy and Clinical Immunology. 2011; 127(2 SUPPL. 1):AB241	Abstract only – food allergy
Dawane JS, Borole KD, Pandit, Salunkhe SD. Parents' knowledge, attitude and perception about the commonly used drugs and their adverse drug reactions in children. International Journal of Pharma and Bio Sciences. 2013; 4(3):461-468	Study focused on adverse drug reactions. Drug allergies not explicitly referred to
DeWitt JE, Sorofman BA. A model for understanding patient attribution of adverse drug reaction symptoms. Drug Information Journal. 1999; 33(3):907-920	Nothing specific to drug allergy
Ewan MA, Greene RJ. Provision of a community pharmacist-run medication advice service at mental health resource centres: A pilot study. Psychiatric Bulletin. 2000; 24(8):294-298	Not relevant to drug allergy
Fagbuyi MA, Joubert G, Diedericks BJS, van Vuuren MVJ. Patients' knowledge and beliefs regarding anaesthetic management [8]. South African Medical Journal. 2002; 92(4):288-289	Letter
Farcas AM, Farah C, Bojita MT. Patients reporting of suspected adverse reactions to antidepressants. A pilot methodological study. Farmacia. 2010; 58(3):255-263	ADR survey
George CF, Waters WE, Nicholas JA. Prescription information leaflets: A pilot study in general practice. British Medical Journal. 1983; 287(6400):1193-1196	1983 study – written information helpful
Golomb BA. Patient reporting of drug adverse effects. Drug Safety. 2010; 33(10):953-954	Abstract only
Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. Drug Saf. 2007; 30(8):669-675	Not question of interest
Gomes ER, Kvedariene V, Demoly P, Bousquet PJ. Patients' satisfaction with diagnostic drug provocation tests and perception of its usefulness. International Archives of Allergy and Immunology. 2011; 156(3):333-338	Not question of interest
Goss FR, Zhou L, Plasek JM, Broverman C, Robinson G, Middleton B et al. Evaluating standard terminologies for encoding allergy information. Journal of the American Medical Informatics Association. 2013; 20(5):969-979	The focus is more on documentation and the outcomes are not relevant to this review
Hadi MA, Helwani R, Long CM. Knowledge and perception of Malaysian hospital pharmacists towards adverse drug reaction reporting: A cross-sectional survey. International Journal of Pharmacy Practice. 2011; 19:18-19	No relevant information on drug allergy – abstract only
Hohl CM, Zed PJ, Brubacher JR, Abu-Laban RB, Loewen PS, Purssell RA. Do emergency physicians attribute drug-related emergency department visits to medication-related problems? Annals of Emergency Medicine. 2010; 55(6):493	Not question of interest
Hopper KD, Houts PS, TenHave TR, Matthews YL, Colon E, Haseman DB et al. The effect of informed consent on the level of anxiety in patients given IV contrast material. American Journal of Roentgenology. 1994; 162(3):531-535	Not question of interest
Kayyali R, Nabhani S, Olszewska A, Adeniyi M. Investigation of bowel and breast cancer patients' perception of counselling and written information provided regarding the oral chemotherapy agent capecitabine. International Journal of Pharmacy Practice. 2012; 20:85-86	Cancer patients
Kennedy A, Lavail K, Nowak G, Basket M, Landry S. Confidence about vaccines in the United States: understanding parents' perceptions. Health Affairs. 2011;	No relevant to drug allergy

Reference	Reason for exclusion
30(6):1151-1159	
King R, Brown L, Weeks R, Roberts G, Erlewyn-Lajeunesse M. Setting up a transition service for young people with food allergy. Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:140	Abstract only – food allergy
Knapp P, Gardner PH, Carrigan N, Raynor DK, Woolf E. Perceived risk of medicine side effects in users of a patient information website: A study of the use of verbal descriptors, percentages and natural frequencies. British Journal of Health Psychology. 2009; 14(3):579-594	Not relevant to drug allergy
Knopf H, Du Y. Perceived adverse drug reactions among non-institutionalized children and adolescents in Germany. British Journal of Clinical Pharmacology. 2010; 70(3):409-417	Not relevant to drug allergy
Konstantelos D, Syriopoulou T, Koulouri A, Athanasopoulou S, Giannakopoulou P, Karli N. Parents' opinions and behaviours regarding antibiotic use by children. Acta Paediatrica, International Journal of Paediatrics. 2010; 99:113	Abstract only
Kroigaard M, Garvey LH, Menne T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? British Journal of Anaesthesia. 2005; 95(4):468-471	Not question of interest
Krska J, Chaipichit N, Chumworathayi P, Jarernsiripornkul N. Strategies to improve patients' knowledge and understanding of drug allergy and behaviour in relation to drug allergy cards in Thailand. Pharmacoepidemiology and Drug Safety. 2013; 22(6):679-680	Conference abstract
Krska J, Morecroft CW. Patients' use of information about medicine side effects in relation to experiences of suspected adverse drug reactions: a cross-sectional survey in medical in-patients. Drug Safety. 2013; 36(8):673-680	Study focused on adverse drug reactions. Drug allergies not explicitly referred to
Lange L, Koningsbruggen SV, Rietschel E. Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children. Pediatric Allergy and Immunology. 2008; 19(7):634-638	Not question of interest
Lauritzen SO. Lay voices on allergic conditions in children: parents' narratives and the negotiation of a diagnosis. Social Science and Medicine. 2004; 58(7):1299-130	Not relevant to drug allergy
Lilja J. The evaluations of drug information programs. Social Science and Medicine. 1985; 21(4):407-414	Narrative review
Marklund B, Ahlstedt S, Nordstrom G. Health-related quality of life in food hypersensitive schoolchildren and their families: parents' perceptions. Health and Quality of Life Outcomes. 2006; 4:48	Not question of interest
Morris LA. A survey of patients' receipt of prescription drug information. Medical Care. 1982; 20(6):596-605	Not question of interest
Nordfeldt S, Hanberger L, Ludvigsson J. Use of a web portal to improve education and communication in young diabetes patients with families - A case study. Pediatric Diabetes. 2011; 12:95	Abstract only
O'Brien BJ, Elswood J, Calin A. Perception of prescription drug risks: a survey of patients with ankylosing spondylitis. Journal of Rheumatology. 1990; 17(4):503-507	Not question of interest
Ola-Olorun OJ, Afolabi MO, Ogunsina AO, Oyebisi TO, Akinyemi OA, Akintomide AO et al. Exploring medicine information needs of hypertensive patients using short message service (SMS) of mobilie phone. Pharmacoepidemiology and Drug Safety. 2012; 21(1):116	Abstract only
O'Neil CK, Poirer TI. Impact of patient knowledge, patient–pharmacist relationship and drug perceptions on adverse drug therapy outcomes. Pharmacotherapy. 1998; 18(2 I):333-340	Not relevant to drug allergy

Reference	Reason for exclusion
Ong D, Popat A, Knowles SR, Arrowood JS, Shear NH, Binkley KE. Objective psychological measurement and clinical assessment of anxiety in adverse drug reactions. Canadian Journal of Clinical Pharmacology. 2004; 11(1):e8-16	Not question of interest
Orhan F, Karakas T, Cakir M, Akkol N, Bahat E, Sonmez FM et al. Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren. Pediatric Allergy and Immunology. 2008; 19(1):82-85	Manifestations only
Peloso C, Safran L, Agranat P, Pailler M-C, Fain O, Fontan J-E et al. Assessment of professional practices: Information provided to patients for management of their chemotherapy side effects. International Journal of Clinical Pharmacy. 2011; 33(2):326	Abstract only
Rathkopf MM, Quinn JM, Proffer DL, Napoli DC. Patient knowledge of immunotherapy before and after an educational intervention: A comparison of 2 methods. Annals of Allergy, Asthma and Immunology. 2004; 93(2):147-153	Not question of interest
Schmiedt D, Ellingson J. Medication education and consultation at a senior dining program for independently living seniors. Consultant Pharmacist. 2010; 25(8):501-510	Not question of interest
Sicherer SH, Vargas PA, Groetch ME, Christie L, Carlisle SK, Noone S et al. Development and validation of educational materials for food allergy. Journal of Pediatrics. 2012; 160(4):651-656	Not relevant to drug allergy
Stewart M, Letourneau N, Masuda JR, Anderson S, McGhan S. Online solutions to support needs and preferences of parents of children with asthma and allergies. Journal of Family Nursing. 2011; 17(3):357-379	The focus is on children with asthma and their parents. The children may have other allergies but not possible to distinguish drug allergies from other allergies
Stewart M, Masuda J, Letourneau N, Anderson S, McGhan S. “I Want to Meet Other Kids Like Me”: Support Needs of Children with Asthma and Allergy. Issues in Comprehensive Pediatric Nursing. 2011; 34(2):62-78	Not question of interest
Stewart M, Letourneau N, Masuda J, Anderson S, McGhan S. Impacts of Online Peer Support for Children With Asthma and Allergies: “It Just Helps You Every Time You Can't Breathe Well”. Journal of Pediatric Nursing. 2013; 28(5):439-452	The focus is on children with asthma and their parents. The children may have other allergies but not possible to distinguish drug allergies from other allergies
Stewart SH, Karp J, Pihl RO, Peterson RA. Anxiety sensitivity and self-reported reasons for drug use. Journal of Substance Abuse. 1997; 9:223-240	Not relevant to drug allergy
Van Haecht CH, Vander Stichele R, Bogaert MG. Package inserts for antihypertensive drugs: use by the patients and impact on adverse drug reactions. European Journal of Clinical Pharmacology. 1990; 39(6):551-554	Not question of interest
Van Haecht CHM, Vander SR, De BG, Bogaert MG. Impact of patient package inserts on patients' satisfaction, adverse drug reactions and risk perception: The case of NSAIDs for posttraumatic pain relief. Patient Education and Counseling. 1991; 17(3):205-215	Not question of interest
van Hunsel F, Harmark L, Pal S, Olsson S, van Grootheest K. Experiences with adverse drug reaction reporting by patients: an 11-country survey. Drug Safety. 2012; 35(1):45-60	Not question of interest
Venkatraghavan S, Rama M, Leelavathi DA. Performance of a drug information centre in a south indian teaching hospital. International Journal of PharmTech Research. 2010; 2(1):390-4	Not question of interest
Vilhelmsson A, Svensson T, Meeuwisse A, Carlsten A. Experiences from	Not question of interest

Reference	Reason for exclusion
consumer reports on psychiatric adverse drug reactions with antidepressant medication: a qualitative study of reports to a consumer association. BMC Pharmacology and Toxicology. 2012; 13:19	
Wagner S, Luskin A, Bukstein D, Kaliner M, Gupta S, Edwards M et al. Self-reported medication adherence in patients with nasal allergies: The disconnect between clinical practice and patient behaviors. Journal of Allergy and Clinical Immunology. 2009; 123(2 SUPPL. 1):S46	Abstract only
Weingart SN, Carbo A, Tess A, Chiappetta L, Tutkus S, Morway L et al. Using a patient internet portal to prevent adverse drug events: a randomized, controlled trial. Journal of Patient Safety. 2013; 9(3):169-175	See documentation rerun
Weingart SN, Pagovich O, Sands DZ, Li JM, Aronson MD, Davis RB et al. What can hospitalized patients tell us about adverse events? Learning from patient-reported incidents. Journal of General Internal Medicine. 2005; 20(9):830-836	Not question of interest
Williams NA, Parra GR, Elkin TD. Parenting children with food allergy: Preliminary development of a measure assessing child-rearing behaviors in the context of pediatric food allergy. Annals of Allergy, Asthma and Immunology. 2009; 103(2):140-145	Not question of interest
Zeigler DK, Mosier MC, Buenaver M, Okuyemi K. How much information about adverse effects of medication do patients want from physicians? Archives of Internal Medicine. 2001; 161(5):706	Study focused on adverse drug reactions. Drug allergies not explicitly referred to

K.6 Non-specialist management – selective COX-2 inhibitors

Reference	Reason for exclusion
Adwan Z. Meloxicam: An alternative treatment in NSAIDs intolerace. Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:290-291	Conference abstract
Andri L, Senna G, Betteli C, Givanni S, Scaricabarozzi I, Mezzelani P et al. Tolerability of nimesulide in aspirin-sensitive patients. Annals of Allergy. 1994; 72(1):29-32	Nimesulide – drug excluded
Anon. More to the management of aspirin-induced asthma than just avoiding aspirin. Drugs and Therapy Perspectives. 2000; 16(5):5-7	Narrative review
Asero R. Multiple sensitivity to NSAID. Allergy. 2000; 55(9):893-894	Drug not in use in UK
Asero R. Predictive value of autologous plasma skin test for multiple nonsteroidal anti-inflammatory drug intolerance. International Archives of Allergy and Immunology. 2007; 144(3):226-230	Subset of participants of an already included study
Asero R. Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. Annals of Allergy, Asthma and Immunology. 1999; 82(6):554-558	Nimesulide – drug excluded
Asero R. Tolerability of rofecoxib. Allergy. 2001; 56(9):916-917	Drug not in use in UK
Barasona VM, Garcia N, I, Medina FA, null, Moreno AC, Guerra PF. Piroxicam, Meloxicam and Celecoxib tolerance in patients with intolerance to nonsteroidal anti-inflammatory drugs: Value of the diagnostic exposure test. Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:290	Conference abstract
Bavbek S, Celik G, Ediger D, Mungan D, Demirel YS, Misirligil Z. The use of nimesulide in patients with acetylsalicylic acid and nonsteroidal anti-inflammatory drug intolerance. Journal of Asthma. 1999; 36(8):657-663	Nimesulide – drug excluded
Bavbek S, Celik G, Pasaoglu G, Misirligil Z. Rofecoxib, as a safe alternative for acetyl salicylic acid/nonsteroidal anti-inflammatory drug-intolerant patients. Journal of Investigational Allergology & Clinical Immunology 2006; 16(1):57-62	Drug not in use in UK
Bennett A. The importance of COX-2 inhibition for aspirin induced asthma.	Narrative review

Reference	Reason for exclusion
Thorax. 2000; 55 Suppl 2:S54-S56	
Berges-Gimeno MP, Camacho-Garrido E, Garcia-Rodriguez RM, Alfaya T, Martin Garcia C, Hinojosa M. Rofecoxib safe in NSAID hypersensitivity. Allergy. 2001; 56(10):1017-1018	Drug not in use in UK
Bianco S, Robuschi M, Petrigni G, Scuri M, Pieroni MG, Refini RM et al. Efficacy and tolerability of nimesulide in asthmatic patients intolerant to aspirin. Drugs. 1993; 46 Suppl 1:115-120	Nimesulide – drug excluded
Blanca M, Dona I, Torres M, Campo P, De BJ, Cornejo J et al. Non steroidal anti-inflammatory drugs (NSAIDS) intolerance versus allergy: Patterns of response and drug involved. Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:294	Abstract – comparison covered by full-text RCT
Campina CS, Neto M, Paris FN, Carvalho F, Trindade M. Nonsteroidal anti-inflammatory drug hypersensitivity: Are single and crossreactors alike? Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:406	Abstract – comparison covered by full-text RCT
Celik G, Erkekol FO, Bavbek S, Dursun B, Misirligil Z. Long-term use and tolerability of cyclooxygenase-2 inhibitors in patients with analgesic intolerance. Annals of Allergy, Asthma & Immunology 2005; 95(1):33-37	All participants had already tolerated a selective COX-2 inhibitor
Di Leo E, Aloia AM, Nettis E, Cardinale F, Foti C, Distaso M et al. Long-term tolerability of etoricoxib in patients with previous reactions to non-steroidal anti-inflammatory drugs. International Journal of Immunopathology and Pharmacology. 2009; 22(4):1131-1134	Retrospective study
Ensina LFC, Bittar RP, Tanno LK, Aun MV, Kalil J, Giavina-Bianchi P et al. Non-steroidal anti-inflammatory drugs hypersensitivity: Patterns of reaction. World Allergy Organization Journal. 2012; 5:S137	Abstract – comparison covered by full-text RCT
Erratum: Rofecoxib, a selective high affinity cox-2 inhibitor, has proved to be safe in urticaria/angioedema associated with NSAIDs intolerance (Allergy: European Journal of Allergy and Clinical Immunology (2001) 56: Supplement 68 (49)). Allergy. 2001; 56(9):912	Drug not in use in UK
Fraj J, Valero A, Vives R, Perez I, Borja J, Izquierdo I et al. Safety of triflusal (antiplatelet drug) in patients with aspirin-exacerbated respiratory diseases. Allergy. 2008; 63(1):112-115	Not addressing review question
Galvez LJ, Anguita CJ, Palacios CL, Saenz De San Pedro Morera, Mayorgas CR. Tolerability to Etoricoxib in anaphilactoid reactions to non steroidal antiinflammatory drugs (NSAIDs). Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:292	Conference abstract
Giuseppe P, Antonino R, Alessandro DB, Donato Q, Marina DF, Donatella P et al. Floctafenine: a valid alternative in patients with adverse reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 1997; 78(1):74-78	Nimesulide – drug excluded
Gomez F, Dona I, Blanca-Lopez N, Torres MJ, Rondon C, Canto G et al. Tolerance to cyclooxigenase-2 selective inhibitors (etoricoxib) in patients with urticaria and angioedema with cross intolerance to non steroidal anti-inflammatory drugs (nsaids). Journal of Allergy and Clinical Immunology. 2010; 125(2 SUPPL. 1):AB158	Abstract – comparison covered by full-text RCT
Hilario MOE, Terreri MT, Len CA. Nonsteroidal anti-inflammatory drugs: cyclooxygenase 2 inhibitors. Jornal De Pediatria. 2006; 82(5 Suppl):S206-S212	Narrative review
Jung J-W, Lim K-H, Kim M-H, Park H-K, Kwon J-W, Kim T-W et al. Hypersensitivity to acetaminophen or celecoxib in patients with aspirin/NSAIDs intolerance. European Annals of Allergy and Clinical Immunology. 2010; 42(2):40-41	Abstract – comparison covered by full-text RCT
Knowles SR, Drucker AM, Weber EA, Shear NH. Management options for patients with aspirin and nonsteroidal antiinflammatory drug sensitivity.	Systematic review – used for cross-referencing

Reference	Reason for exclusion
Annals of Pharmacotherapy. 2007; 41(7-8):1191-1200	
Koti I, Makris M, Chliva C, Aggelides X, Chatziioannou A, Kalogeromitros D. Clinical aspects and outcomes of oral challenges to non-steroidal anti-inflammatory drugs. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:50	Abstract – comparison covered by full-text RCT
Kruse R, Ruzicka T, Grewe M. Intolerance reactions due to the selective cyclooxygenase type II inhibitors rofecoxib and celecoxib. Results of oral provocation tests in patients with NSAID hypersensitivity. Acta Dermato-Venereologica. 2003; 83(3):183-185	Drug not in use in UK and case series
Llanora GV, Gerez IFA, Cheng YK, Shek LPC. Etoricoxib: A probable safe alternative for NSAID intolerant patients in Asia. Journal of Allergy and Clinical Immunology. 2012; 129(2 SUPPL. 1):AB105	Conference abstract
Llanora GV, Loo EXL, Gerez IF, Cheng YK. Etoricoxib: a safe alternative for NSAID intolerance in Asian patients. Asian Pacific Journal of Allergy and Immunology. 2013; 31(4):330-333	Unclear description of methods: most likely to be a retrospective study
Malskat WS, Knulst AC, Bruijnzeel-Koomen CA, Rockmann H. Tolerance to alternative cyclooxygenase-2 inhibitors in nonsteroidal anti-inflammatory drug hypersensitive patients. Clinical and Translational Allergy. 2013; 3(1):20	Not addressing review question
Martin-Garcia C, Hinojosa M, Berges P, Camacho E, Garcia-Rodriguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. Journal of Investigational Allergology and Clinical Immunology. 2003; 13(1):20-25	Drug not in use in UK
Massaccesi C, Stagnozzi G, Frontini F, Braschi C, Brianzoni F, Bilo M. Tolerance of etoricoxib in patients with different types of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:606	Abstract – comparison covered by full-text RCT
Matucci A, Parronchi P, Vultaggio A, Rossi O, Brugnolo F, Maggi E et al. Partial safety of the new COX-2 inhibitor rofecoxib in NSAIDs high sensitive patients. Allergy. 2004; 59(10):1133-1134	Drug not in use in UK
Micheletto C, Tognella S, Guerriero M, Dal Negro R. Nasal and bronchial tolerability of Rofecoxib in patients with aspirin induced asthma. European Annals of Allergy and Clinical Immunology. 2006; 38(1):10-14	Drug not in use in UK
Mielgo R, Daroca P, Romero V, Fernandez C, Alcorta A, Jimenez A. Tolerance to paracetamol, meloxicam and etoricoxib in patients intolerant to non-steroidal antiinflammatory drugs. Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:606	Conference abstract
Moriya M, Aihara M, Ikezawa Z. Analysis of clinical diversity of urticaria and angioedema induced by non-steroidal anti-inflammatory drugs (NSAIDs) in Japan. European Annals of Allergy and Clinical Immunology. 2010; 42(2):88-89	Abstract – comparison covered by full-text RCT
Nettis E, Colanardi MC, Ferrannini A, Tursi A. Immune tolerance to drugs. (II).: Long-term tolerability of nimesulide in patients with NSAID hypersensitivity. Immunopharmacology and Immunotoxicology. 2004; 26(3):469-480	Drug not in use in UK
Nettis E, Colanardi MC, Ferrannini A, Tursi A. Short-term and long-term tolerability of rofecoxib in patients with prior reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 2005; 94(1):29-33	Drug not in use in UK
Nettis E, Di Paola R, Napoli G, Ferrannini A, Tursi A. Benzydamine: an alternative nonsteroidal anti-inflammatory drug in patients with nimesulide-induced urticaria. Allergy. 2002; 57(5):442-445	Drug not in use in UK
Nettis E, Di PR, Ferrannini A, Tursi A. Tolerability of rofecoxib in patients with cutaneous adverse reactions to nonsteroidal anti-inflammatory drugs. Annals of Allergy, Asthma and Immunology. 2002; 88(3):331-334	Drug not in use in UK

Reference	Reason for exclusion
Nettis E, Marcandrea M, Ferrannini A, Tursi A. Tolerability of nimesulide and paracetamol in patients with NSAID-induced urticaria/angioedema. Immunopharmacology and Immunotoxicology. 2001; 23(3):343-354	Nimesulide – drug excluded
Nosbaum A, Braire M, Dubost R, Chantel S, Nicolas JF, Berard F. Cutaneous NSAID intolerance does not prevent the intake of normal doses of NSAID. European Annals of Allergy and Clinical Immunology. 2010; 42(2):77	Abstract – comparison covered by full-text RCT
Novotna B, Kroupa R. Tolerability of etoricoxib (cyclooxygenase 2 selective inhibitor) in patients with acetylsalicylic acid and or nonsteroidal antiinflammatory drugs sensitivity. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:160	Abstract – comparison covered by full-text RCT
Pacor ML, Di Lorenzo G, Biasi D, Barbagallo M, Corrocher R. Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or non-steroidal anti-inflammatory drugs. Clinical and Experimental Allergy. 2002; 32(3):397-400	Drug not in use in UK
Pastorello EA, Zara C, Riario-Sforza GG, Pravettoni V, Incorvaia C. Atopy and intolerance of antimicrobial drugs increase the risk of reactions to acetaminophen and nimesulide in patients allergic to nonsteroidal anti-inflammatory drugs. Allergy. 1998; 53(9):880-884	Drug not in use in UK
Perrone MR, Artesani MC, Viola M, Gaeta F, Caringi M, Quaratino D et al. Tolerability of rofecoxib in patients with adverse reactions to nonsteroidal anti-inflammatory drugs: a study of 216 patients and literature review. International Archives of Allergy and Immunology. 2003; 132(1):82-86	Drug withdrawn from use in UK
Picado P. COX-2 specific inhibitors in NSAID-intolerant patients. International Journal of Immunopathology and Pharmacology. 2003; 16(2 Suppl):11-16	Conference abstract
Quaratino D, Romano A, Papa G, Di Fonso M, Giuffreda F, D'Ambrosio FP et al. Long-term tolerability of nimesulide and acetaminophen in nonsteroidal antiinflammatory drug-intolerant patients. Annals of Allergy, Asthma and Immunology. 1997; 79(1):47-50	Nimesulide – drug excluded
Quinones Estevez MD. Are selective COX-2 inhibitors a safe option in patients with intolerance to nonsteroidal antiinflammatory drugs? Journal of Investigational Allergology and Clinical Immunology. 2009; 19(4):328-330	Case series – research design not included in protocol
Quiralte J, Saenz de San Pedro B, Florido JJF. Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. Annals of Allergy, Asthma and Immunology. 2002; 89(1):63-66	Drug not in use in UK
Reis FA, Santos N, Botelho C, Castro E, Cernadas R. Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs: Single versus multiple reactors. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:51-52	Abstract – comparison covered by full-text RCT
Ribeiro F, Almeida E, Sousa N, Faria E, Carrapatoso I, Segorbe LA. Cutaneous hypersensitivity to non-steroidal antiinflammatory drugs. Allergy: European Journal of Allergy and Clinical Immunology. 2012; 67:129	Abstract – comparison covered by full-text RCT
Rondon C, Dona I, Gomez F, Blanca-Lopez N, Torres MJ, Laguna JJ et al. Tolerance to etoricoxib in patients with urticaria and/or angioedema with cross intolerance to non steroidal anti-inflammatory drugs (NSAIDs). European Annals of Allergy and Clinical Immunology. 2010; 42(2):90	Abstract – comparison covered by full-text RCT
Sanchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Tolerance of nonsteroidal anti-inflammatory drug-sensitive patients to the highly specific cyclooxygenase 2 inhibitors rofecoxib and valdecoxib. Annals of Allergy, Asthma and Immunology. 2005; 94(1):34-38	Drugs not in use in UK
Senna GE, Passalacqua G, Andri G, Dama AR, Albano M, Fregonese L et al. Nimesulide in the treatment of patients intolerant of aspirin and other NSAIDs. Drug Safety. 1996; 14(2):94-103	Nimesulide – drug excluded
Stevenson DD, Simon RA. Lack of cross-reactivity between rofecoxib and	Drug not in use in UK

Reference	Reason for exclusion
aspirin in aspirin-sensitive patients with asthma. Journal of Allergy and Clinical Immunology. 2001; 108(1):47-51	
Stevenson DD, Zuraw BL. Pathogenesis of aspirin-exacerbated respiratory disease. Clinical Reviews in Allergy and Immunology. 2003; 24(2):169-188	Background reading purposes only
Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M. Safety of a specific COX-2 inhibitor in aspirin-induced asthma. Clinical and Experimental Allergy. 2001; 31(2):219-225	Drug not in use in UK
Tanno L, Aun M, Ensina L, Aun-Pereira V, Itokazu C, Yamashita M et al. COX-2 inhibitor provocation tests in non-steroidal anti-inflammatory drugs hypersensitivity patients: Analysis of safety and cross-reactivity. Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:64	Abstract – comparison covered by full-text RCT
Trombetta D, Imbesi S, Vita G, Isola S, Minciullo PL, Saija A et al. Possible link between history of hypersensitivity to a specific non-steroidal anti-inflammatory drug (NSAID) and positive results following challenge test to alternative NSAIDS. Arzneimittel-Forschung. 2009; 59(8):410-414	Retrospective study; all participants known to have sensitivity to selective COX-2 inhibitors
Tudose A, Gheonea C, Vieru M, Popescu F. Etoricoxib short-term safety profile in aspirin-aggravated autoreactive chronic urticaria. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:108	Abstract – comparison covered by full-text RCT
Tudose A, Popescu S, Vieru M, Popescu F. Etoricoxib for acute dental pain in patients with autoimmune chronic urticaria and non-selective non-steroidal anti-inflammatory drug hypersensitivity. Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:267	Abstract – comparison covered by full-text RCT
Valero A, Baltasar M, Enrique E, Pau L, Dordal MT, Cistero A et al. NSAID-sensitive patients tolerate rofecoxib. Allergy. 2002; 57(12):1214-1215	Drug not in use in UK
Valero Santiago A, Gonzalez-Morales MA, Marti Guadano E, (GETNIA) Grupo de Estudio de Tolerancia. Tolerance of nimesulide in NSAID intolerant patients. Allergy. 2003; 58(4):367-368	Drug not in use in UK
Vázquez-Cortés S, Vázquez-Fuertes L, Rodríguez-Alvarez M, Reig Rincón dA, I, Martínez-Cócera C. [Tolerance to celecoxib and meloxicam in patients with intolerance to nonsteroidal anti-inflammatory drugs]. Anales De Medicina Interna (Madrid, Spain. 2008; 25(4):163-167	Study not in English
Viola M, Quaratino D, Gaeta F, Rumi G, Caruso C, Romano A. Cross-reactive reactions to nonsteroidal anti-inflammatory drugs. Current Pharmaceutical Design. 2008; 14(27):2826-2832	Narrative review
Weberschock TB, Muller SM, Boehncke S, Boehncke WH. Tolerance to coxibs in patients with intolerance to non-steroidal anti-inflammatory drugs (NSAIDs): a systematic structured review of the literature. Archives of Dermatological Research. 2007; 299(4):169-175	Systematic review – used for cross-referencing
West PM, Fernandez C. Safety of COX-2 inhibitors in asthma patients with aspirin hypersensitivity. Annals of Pharmacotherapy. 2003; 37(10):1497-1501	Systematic review – used for cross-referencing
Woessner KM, Simon RA, Stevenson DD. Safety of high-dose rofecoxib in patients with aspirin-exacerbated respiratory disease. Annals of Allergy, Asthma and Immunology. 2004; 93(4):339-344	Drug not in use in UK
Yilmaz O, Ertoy Karagol IH, Bakirtas A, Topal E, Celik GE, Demirsoy MS et al. Challenge-proven nonsteroidal anti-inflammatory drug hypersensitivity in children. Allergy: European Journal of Allergy and Clinical Immunology. 2013; 68(12):1555-1561	Abstract: fully published evidence sufficiently available
Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, Szczeklik A. Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. Archives of Dermatology. 2003; 139(12):1577-1582	Drug not in use in UK

K.7 Referral to specialist drug allergy services

Reference	Reason for exclusion
Al-Ahmad MS, Arifhodzic N, Al AN, Al-Onizi A, Fakim N. Penicillin allergy evaluation: Experience from a drug allergy clinic in Kuwait. Journal of Allergy and Clinical Immunology. 2011; 127(2 SUPPL. 1):AB251	Abstract
Araujo L, Demoly P. Provocation tests in drug allergy. Revista Portuguesa De Imunoalergologia. 2009; 17(4):315-324	Background narrative
Baccioglu A, Kalpaklioglu A. Drug allergy: The physician's and the patient's perspective. Allergy: European Journal of Allergy and Clinical Immunology. 2009; 64:401	Abstract
Begin P, Picard M, Bouchard H, Cloutier J, Daoust E, Paradis L et al. Quality of penicillin allergy management in the intensive care unit and internal medicine ward. Allergy, Asthma and Clinical Immunology. 2010; 6	Conference abstract
Bellou A, Manel J, Samman-Kaakaji H, De Korwin JD, Moneret-Vautrin DA, Bollaert P-E et al. Spectrum of acute allergic diseases in an emergency department: An evaluation of one years' experience. Emergency Medicine. 2003; 15(4):341-347	Does not address question of interest directly. Provides only indirect evidence
Biagtan M, Kakumanu S, Mathur SK. Characterization of penicillin allergy among VA patients. Journal of Allergy and Clinical Immunology. 2013; 131(2 SUPPL. 1):AB173	Abstract
Buchmiller BL, Khan DA. Evaluation and management of pediatric drug allergic reactions. Current Allergy and Asthma Reports. 2007; 7(6):402-409	Narrative review
Caubet J-C, Eigenmann PA. Managing possible antibiotic allergy in children. Current Opinion in Infectious Diseases. 2012; 25(3):279-285	Not question of interest
Church H, Kong K, North J. A review of the first year of data from a bi-speciality anaesthetic allergy clinic in the West Midlands, UK. European Journal of Anaesthesiology. 2009; 26:206	Abstract
Confino-Cohen R, Leader A, Klein N, Pereg D, Khoury S, Perl L et al. Drug allergy in hospitalized patients: the contribution of allergy consultation and a structured questionnaire. International Archives of Allergy and Immunology. 2012; 158(3):307-312	Not question of interest
Dordal CM, Romero DM, Marti GE, Rietti JS, Freixas LM, Ancochea SL et al. Allergy in primary care: A pilot experience in the city of Barcelona (Catalonia, Spain). Allergy: European Journal of Allergy and Clinical Immunology. 2010; 65:144	Abstract
Erdeljic V, Francetic I, Likic R, Bakran I, Makar-Ausperger K, Simic P. Is referring patients with a positive history of allergic drug reactions or atopy for allergy testing to local anesthetics justified? Methods and Findings in Experimental and Clinical Pharmacology. 2009; 31(3):177-182	Patient population limited to those with atopy or or history of ADR to drugs other than LA
Ewan PW. Provision of allergy care for optimal outcome in the UK. British Medical Bulletin. 2000; 56(4):1087-1101	Narrative review
Forrest DM, Schellenberg RR, Thien V, V, King S, Anis AH, Dodek PM. Introduction of a practice guideline for penicillin skin testing improves the appropriateness of antibiotic therapy. Clinical Infectious Diseases. 2001; 32:1685-1690	Does not address question of interest directly. Provides only indirect evidence.
Fulton RB, Judelman S, Rose M, Fernando SL. Morphine and pholcodine specific IGE testing for the investigation of suspected anaesthesia associated anaphylaxis to neuromuscular blocking agents. Internal Medicine Journal. 2010; 40:9-10	Abstract
Hippern LD, Halapy H. Assessing penicillin allergies with a structured assessment form. Canadian Journal of Hospital Pharmacy. 2000; 53(3):184-192	Does not address question of interest directly. Provides only indirect

Reference	Reason for exclusion
	evidence
Jost BC, Wedner HJ, Bloomberg GR. Elective penicillin skin testing in a pediatric outpatient setting. Annals of Allergy, Asthma and Immunology. 2006; 97(6):807-812	Not question of interest
Kalogeromitros D, Rigopoulos D, Gregoriou S, Papaioannou D, Mousatou V, Katsarou-Katsari A. Penicillin hypersensitivity: value of clinical history and skin testing in daily practice. Allergy and Asthma Proceedings. 2004; 25(3):157-160	Does not address question of interest directly. Provides only indirect evidence
Kaminski E. An audit of referrals to a regional allergy clinic with suspected penicillin allergy. Clinical and Experimental Allergy. 2011; 41(12):1835	Abstract
Karabus SJ, Motala C, Joshua B. Penicillin allergy in children - Often misdiagnosed? Journal of Allergy and Clinical Immunology. 2009; 123(2 SUPPL. 1):S240	Abstract
Kerbelker T, Levin ME. Penicillin allergy at a tertiary centre in Cape Town, South. Journal of Allergy and Clinical Immunology. 2013; 131(2 SUPPL. 1):AB174	Abstract
Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A et al. Early presentation with angioedema and urticaria in cross-reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. Pediatrics. 2005; 116(5):e675-e680	Not question of interest
Langley JM, Halperin SA, Bortolussi R. History of penicillin allergy and referral for skin testing: evaluation of a pediatric penicillin allergy testing program. Clinical and Investigative Medicine Medecine Clinique Et Experimentale. 2002; 25(5):181-184	Not question of interest
Liccardi G, Lobefalo G, Di Florio E, Di Iorio C, Occhiochiuso L, Romano L et al. Strategies for the prevention of asthmatic, anaphylactic and anaphylactoid reactions during the administration of anesthetics and/or contrast media. Journal of Investigational Allergology and Clinical Immunology. 2008; 18(1):1-11	Background narrative
Lu DP. Managing patients with local anesthetic complications using alternative methods. Pennsylvania Dental Journal. 2002; 69(3):22-29	Narrative
Macy E. Elective penicillin skin testing and amoxicillin challenge: effect on outpatient antibiotic use, cost, and clinical outcomes. Journal of Allergy and Clinical Immunology. 1998; 102(2):281-285	Does not address question of interest directly. Provides only indirect evidence
McClimon BJ, Li JT, Ferguson B, Markus P, Odell L, Swanson A et al. Allergist and pharmacist collaboration increases beta-lactam antibiotic use in patients with a history of penicillin allergy. Journal of Allergy and Clinical Immunology. 2009; 123(2 SUPPL. 1):S212	Abstract
Mulder WMC, Meinardi MMHM, Van Boxtel CJ. Outpatient clinic for drug related problems. International Journal of Risk and Safety in Medicine. 2004; 16(3):171-176	Referral not allergy related
Park MA, McClimon BJ, Ferguson B, Markus PJ, Odell L, Swanson A et al. Collaboration between allergists and pharmacists increases -lactam antibiotic prescriptions in patients with a history of penicillin allergy. International Archives of Allergy and Immunology. 2011; 154(1):57-62	Universal testing of patients with PCN allergy – pharmacist referral on basis of history in chart
Patel B, Mason P, Kakumanu S, Mathur SK. Aspirin allergy in a VA population: Is there potential benefit for evaluation in the allergy clinic? Journal of Allergy and Clinical Immunology. 2013; 131(2 SUPPL. 1):AB167	Does not address question of interest directly. Provides only indirect evidence
Patel N, Warner JO, Gore C. Itchy 'sneezy' wheezy survey: How do referral reasons to allergy clinic compare to diagnoses made at first allergy clinic visit?	Conference abstract

Reference	Reason for exclusion
Clinical and Experimental Allergy. 2012; 42(12):1835	
Philipson EH, Lang DM, Gordon SJ, Burlingame JM, Emery SP, Arroliga ME. Management of group B Streptococcus in pregnant women with penicillin allergy. Journal of Reproductive Medicine. 2007; 52(6):480-484	Does not address question of interest directly. Provides only indirect evidence
Phillips E, Louie M, Knowles SR, Simor AE, Oh P, I. Cost-effectiveness analysis of six strategies for cardiovascular surgery prophylaxis in patients labeled penicillin allergic. American Journal of Health-System Pharmacy. 2000; 57:339-345	Does not address question of interest directly. Provides only indirect evidence
Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. Journal of Pediatrics. 1998; 132(1):137-143	Does not address question of interest directly. Provides only indirect evidence
Pineda R, Lezcano PM, Fernandez T, Zambrano G, Pelta R, Barrio MD. Non-immediate hypersensitivity reactions to non-steroideal anti-inflammatory drugs (NSAIDs). Journal of Allergy and Clinical Immunology. 2013; 131(2 SUPPL. 1):AB168	Abstract
Ponvert C, Perrin Y, Bados-Albiero A, Le Bourgeois M, Karila C, Delacourt C et al. Allergy to betalactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests. Pediatric Allergy and Immunology. 2011; 22(4):411-418	Does not address question of interest directly. Provides only indirect evidence
Prematta T, Ishmael F. Physician approaches to beta-lactam use in patients with penicillin hypersensitivity. Journal of Allergy and Clinical Immunology. 2011; 127(2 SUPPL. 1):AB190	Survey of prescribing habits
Puchner TCJ, Zacharisen MC. A survey of antibiotic prescribing and knowledge of penicillin allergy PUCHNER2002. Annals of Allergy, Asthma and Immunology. 2002; 88(1):24-29	Prescribing habits
Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. Annals of Emergency Medicine. 2009; 54(1):72-77	No gold standard comparison. Not question of interest
Rebelo Gomes E, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. Clinical and Experimental Allergy. 2008; 38(1):191-198	Does not address question of interest directly. Provides only indirect evidence
Redelmeier DA, Sox HCJ. The role of skin testing for penicillin allergy. Archives of Internal Medicine. 1990; 150(9):1939-1945	Theoretical statistical model in USA – not relevant assumptions to UK
Sagar PS, Katelaris CH. The prevalence of true penicillin allergy from a study of cases at campbelltown hospital immunology clinic. Internal Medicine Journal. 2011; 41:17	Abstract
Scully P, Roche D, O'Donnell B, McAlister S, O'Connor M, Peters C et al. Elderly admissions following primary care referral: The truth is in the referring. Irish Journal of Medical Science. 2013; 182:S276-S277	Conference abstract
Seitz CS, Brocker EB, Trautmann A. Diagnosis of drug hypersensitivity in children and adolescents: discrepancy between physician-based assessment and results of testing. Pediatric Allergy and Immunology. 2011; 22(4):405-410	Details of history taking and referral criteria not described
Sturm J, Temprano J. A survey of current physician practice and knowledge of drug allergy at a university medical center. Journal of Allergy and Clinical Immunology. 2012; 129(2 SUPPL. 1):AB99	Abstract
Tamayo E, Rodriguez-Ceron G, Gomez-Herreras JI, Fernandez A, Castrodeza J,	Details of history taking

Reference	Reason for exclusion
Alvarez FJ. Prick-test evaluation to anaesthetics in patients attending a general allergy clinic. European Journal of Anaesthesiology. 2006; 23(12):1031-1036	not described
Tanno LK, Curi SV, Fernandes F, Dracoulakis M, Aun WT, Mello JF. Drug hypersensitivity reactions in hospitalized patients: What is the role of the allergist? World Allergy Organization Journal. 2012; 5:S141	Abstract
Webb L-A, Jones CJ, Smith HE. An audit of the recording of adverse drug reactions and allergies in GP elective referral letters to specialists. Clinical and Experimental Allergy. 2012; 42(12):1831-1832	Conference abstract
Williams A, Joyce M, Rajakulasingam K. Do patient histories in general practitioner referral letters predict penicillin allergy in a specialist drug allergy clinic? Allergy: European Journal of Allergy and Clinical Immunology. 2011; 66:178-179	Abstract
Wohrl S, Vigl K, Stingl G. Patients with drug reactions -- is it worth testing? Allergy. 2006; 61(8):928-934	Does not address question of interest directly. Provides only indirect evidence
Wong BBL, Keith PK, Waserman S. Clinical history as a predictor of penicillin skin test outcome. Annals of Allergy, Asthma and Immunology. 2006; 97(2):169-174	Does not address question of interest directly. Provides only indirect evidence

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Appendix L: Excluded economic studies

There are no excluded economic studies for this guideline.

Appendix M: Research recommendations

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M.1 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 intra-dermal tests) to a diagnostic oral antibiotic challenge rather than refer to specialist drug allergy services?

Why is this important?

Antibiotics are an important class of drug and one of the most common groups of drugs prescribed to children. Many childhood illnesses are associated with skin rashes, and it can be clinically difficult in the acute setting to be certain if an atypical rash is caused by the underlying illness, the antibiotic, or both. Adverse drug reactions to antibiotics are common and frequently result in a child being diagnosed with 'drug allergy', a diagnosis which generally remains for life.

Current clinical experience suggests that most patients in a community setting who are believed to be allergic to an oral antibiotic (approximately 3% for children, 10–20% for adults) will be challenge 'negative' – that is, they are able to tolerate the oral antibiotic on the day of the challenge and on subsequent days. While patients who are correctly diagnosed with an allergy are kept safe through avoidance, there are health and cost implications for patients who are incorrectly diagnosed with an antibiotic allergy.

The evidence review for this clinical guideline found no evidence to support the reliability of allergy testing (skin, intradermal or IgE determination) for the diagnosis of antibiotic allergy in children. In addition, these tests are painful and restricted to only a few specialist centres in the UK. The result is that only a small fraction of children in the UK with a diagnosis of antibiotic allergy ever undergo investigations to confirm or exclude this diagnostic 'label'. It would therefore be beneficial to prospectively investigate the use of the oral supervised challenge in a safe clinical setting without prior allergy testing. This novel diagnostic approach could be compared with an intervention of 'antibiotic avoidance'.

If the oral antibiotic challenge is found to be safe, acceptable and cost effective, it could be rolled out across all centres that offer paediatric allergy services. This would reduce substantially the number of children who receive a lifelong label of antibiotic allergy.

Population	Inclusion Criteria: 1. All children and young people under the age of 16 who have had non-systemic mild maculopapular reactions, within 2 days of commencing treatment with an oral antibiotic. Sampling population: Patients will be identified in routine allergy clinics but also on GP databases. Parent or guardian willing to provide informed written consent Exclusion Criteria: 2. Clinically significant concomitant medical illness e.g. unstable asthma, renal disease 3. Previous anaphylaxis (any) Setting: Children's Drug Allergy Service at Guys and St Thomas' NHS Foundation Trust, London
Intervention	Supervised, incremental dose oral antibiotic administration; to be followed by administration over the subsequent 2 days (if supervised challenge negative)

	This represents a diagnostic strategy.
Comparator(s)	The 'active' intervention is to be compared to children on a waiting list for referral to specialist drug allergy services. If not referred by 12 month follow-up the waiting list group will then be offered a diagnostic antibiotic challenge.
Outcome	1) Acceptability: of this diagnostic process to parents and carers, that is, do parents and carers consent to undergoing this investigation (in the absence of SPT, intradermal and IgE testing). 2) Determine the number of children who return for follow-up and reasons for non-returners. 3) Assess the long term acceptability of this diagnostic process with regards to future antibiotic use i.e. was the antibiotic taken (if challenge negative) or avoided (if challenge positive). 4) Quality of life: comparison between group randomised to undergo sooner challenge and group randomised to no intervention for 12 months before challenge 5) Diagnostic accuracy. Diagnostic outcomes will be scored using a set of a priori criteria as positive, negative, or equivocal. These assessments are to be made acutely (on day of challenge and during subsequent 2 days of therapy) and after an interval follow up where assessments will be made of repeat antibiotic exposure. 6) The safety of the procedure at following time points (i) day of challenge (ii) with subsequent ingestion over 2 days and (iii) with repeat exposure/avoidance during follow up interval in initial 50 challenges. Diagnostic value (incidence of negative and positive challenges) at time periods (i), (ii) and (III) – see above. 7) Cost: Cost estimates will be compared between the 2 groups. Cost variables will include staffing, ward costs, alternate antibiotic use costs, costs of adverse effects related to antibiotic use and other medical complications in both groups.
Study Design	Single centre (GSTT) Randomised trial Total n =100; 50 children will be randomised to soonest possible challenge (active group) and 50 will adopt an active avoidance approach for 12 months and then undergo challenge (passive group). Patients will predominantly be enrolled from GP databases where criteria are met for the possible diagnosis of an oral antibiotic allergy. Patients who meet severe criteria (as per NICE document +++) will be excluded. This study will also serve to validate the use of those criteria, at least for children and for antibiotic reactions.
Timeframe	Initial study design and ethics application 4 months. Initial 50 challenges 12 months;' subsequent 50 challenges in group randomised to avoidance, 6 months. Total duration = 2 years.
Importance to patients or the population	A negative drug challenge will result in the removal of the 'antibiotic allergy' diagnosis for the participant's medical records. This has favourable implications for the individual (more appropriate, possibly safer, antibiotic choices), health system (reduced cost) and society (reduction in antibiotic resistance that may arise when other antibiotics are used) Of the 3% of participants who do experience symptoms these are likely to be mild and easily managed and for these children a positive challenge outcome facilitates safer antibiotic choices for their future care.

Relevance to NICE guidance	This is relevant to NICE guidance since evidence to support the use of skin testing and IgE testing to oral antibiotics (in the clinical setting we describe, that is, milder reactions) was found to be weak, or non-existent for children. If this study demonstrates that patients may safely proceed to an oral supervised challenge (if initial safe criteria are met), and that the majority of challenge outcomes are negative, then this will prove of great diagnostic importance and thereby influence future NICE guidelines.
Relevance to the NHS	The management strategy would represent a cost effective, novel and safe diagnostic investigation. Appropriate clinical space would be needed to perform the challenges.
National priorities	This is relevant since it could lead to long term cost savings and the use of cephalosporins, as an alternative to penicillins, is associated with drug resistance to this important class of antibiotics. Addressing the issue of drug resistance has been highlighted as a major public concern by the NHS.
Current evidence base	Data is limited with regard to the appropriate diagnostic strategy in the above scenario in children and young people. Allergy societies do not make firm diagnostic recommendations for this subgroup. Skin tests and intradermal tests are poorly tolerated by younger children and require some expertise to perform and interpret. Such testing is offered by very few specialist centres. There are no known ongoing trials.
Equality	Care has to be taken to provide both parents (or guardians) as well as children with accessible information about the study in order to be able to discuss possible worries about the safety with each other and health care professionals before consenting to take part. It is important to ensure that the child is not pressured by anyone to take part in the study.
Feasibility	Yes, approximately 2 years. Sample size: In this population; rate of true allergy though to be around 3%. To obtain a 95% CI of 1–6% rates of reactivity this should hopefully be achieved with an initial sample of n=100 . The current standard of care is for an antibiotic allergy label to apply, for example ‘penicillin allergy’, and this is usually life-long. We argue that this approach is potentially associated with negative health outcomes, both for the individual as well as society at large. Oral challenges will be assessed for safety; oral antibiotic, when taken orally, despite widespread use, has not been associated with IgE-mediated fatalities, and we will not be making assessment of delayed reactions (which can be associated with adverse outcomes and even fatalities)
Other comments	We are aware that due to a risk of allergic drug reactions to participating children clear protocol principles will be central in the study design in line with the UK research ethics.

M.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?

Why is this important?

Administering drugs to which patients have a reported allergy can be fatal, but inadvertent prescription or administration of such drugs is common. Data from the UK General Practice Research Database indicate that the incidence of contraindicated antibiotics being re-prescribed to patients with suspected penicillin allergy is as high as 48.5%, suggesting that even electronic systems with reminders do not eliminate the risk of inappropriate prescribing. Also, few allergy documentation systems communicate across healthcare organisations, so this information may be lost when patients move to new areas.

Patients and their families and carers have been identified as a resource to prevent inappropriate prescribing. This is in line with the concept of 'patient responsibility' described in the NHS Constitution (2010). Patients and their families and carers are encouraged to be involved in decisions about their care and this includes decisions about drug choice. However, in current practice information is usually not provided unless drug allergy is confirmed by specialists. Suitable information provision is important to encourage people to volunteer their allergy status (be it suspected or confirmed) and make sure that this is appropriately documented by healthcare professionals.

The British Society for Allergy and Clinical Immunology (BASCI) recommends giving patients written details about their allergy, including information on drugs they should avoid. However, it is unclear what factors influence patients to disclose their allergy status to healthcare professionals and what would empower them to do so, to improve safety.

Research is therefore needed to determine which information strategy would be most effective (and preferred by patients) to:

- increase patients' knowledge about their allergy and ability to remember this information
- increase patient empowerment and confidence to discuss their drug allergy with healthcare professionals
- minimise harm from inadvertent re-exposure to a suspected drug allergen.

Population	All adult patients who receive drug treatment in the NHS who report a suspected drug allergy, and parents or carers of children or vulnerable adults with drug allergies. 'Diagnosis disease stage' is any point at which drug allergies are assessed or discussed, for example first presentation at the healthcare organisation or at the start of a new care episode. Exclusion criteria: patients in whom the symptoms described are adverse effects only, not allergy. All settings including community, secondary care and specialist allergy clinics.
Intervention	Patient-focused information leaflet (describing communication about drug allergies, situations in which information about people's allergy should be disclosed and providing real life examples with descriptions of people's experiences).
Comparator(s)	Current routine NHS care. This is generally no formal information provided, unless allergy has been proven in formal allergy testing (in which case it would most often be verbal information or occasionally a general factsheet).
Outcome	• frequency of drug allergy notification provided by the person to healthcare professionals • change in the person's perceived level of empowerment • frequency of prescriptions for the drug a person is allergic to. • number of allergic reactions in each group

	• appropriate or inappropriate avoidance of drugs • Quality of life • cost
Study Design	Randomised controlled trial
Timeframe	Follow-up times need to be sufficiently for outcomes to appear (for example, future appointments with healthcare professionals, change in feelings of empowerment). Most likely that would mean 6- and 12-months follow-up.
Importance to patients or the population	Medication incident reports and research indicate that the current NHS systems provide ineffective safeguards to address the risk of prescribing drugs to which patients report allergy. Patients reporting drug allergies or suspected drug allergies should be given information about their reported allergy in an accessible way. Appropriate information may empower people in being more involved and proactive in decisions about their care.
Relevance to NICE guidance	Having evidence indicating which factors of information strategies influence patients' empowerment to discuss their allergies is of high importance as it will inform future recommendations in updates to the guideline.
Relevance to the NHS	It is relevant to the NHS since improvements in information provision would lead to more effective interactions between the person with suspected or confirmed drug allergy and healthcare professionals. Minimising future harms from drug allergies will lead to reputational, financial (including litigation), operational, patient and staff benefits.
National priorities	The current NHS Outcomes Framework 2013–2014 identifies minimising serious harms arising from unsafe use of medicines as a priority, including inadvertent prescription of drugs to which patients report allergy. Patient responsibility for their care is described in the NHS Constitution (2010). This includes involvement in decisions about their care and medication. The British Society for Allergy for Clinical Immunology (BASCI) recommends that patients be given written details about their allergy, including medicines to avoid
Current evidence base	A systematic review on patient information was carried out for this guideline and concluded that people with suspected or confirmed drug allergies felt that the information currently provided could be improved on, and that interactions with health care professionals were not always effective or empowering.
Equality	Equality issues arising in this research recommendation may relate to accessible formats of the information provided (for example for patients with visual impairment or low literacy). This could be overcome by the use of trained facilitators who would ensure that the information format provided is suitable for the person needs. Using a randomised controlled design would allow protocols to be designed to make the information accessible to all participants.
Feasibility	The proposed research could be carried out within timescales of between 1–2 years (recruitment to follow-up). Such a study would require relatively small sample sizes. The expense is likely to be low, examples being printed materials. There are no ethical issues as long as information is provided in an accessible format with interpretation if necessary.
Other comments	These are very important patient safety research questions to provide evidence to enhance patient engagement in their care and solutions to the poor communication between organisations.

M.3 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?

Why is this important?

Evidence from patient safety incident reports to the National Reporting and Learning System and from published research shows that a large number of NHS patients with known drug allergies are being re-exposed to these drugs in error each year. Over the past few decades, many people have been inaccurately diagnosed and recorded as either having or not having a drug allergy. Whilst re-exposure to a drug has not caused harm in the majority of people, a minority of these incidents have caused harm or death.

The systematic review undertaken for this guideline identified a wide range of documentation strategies, including patient-held records; information worn by patients; hospital-based notices worn by patients (such as coloured arm bands); automated messages (for example, screen savers); mandatory reporting of drug allergy status in paper or electronic medication records; mandatory documentation of details related to adverse drug reactions; design of drug charts; use of Summary of Care Records; and computerised physician or prescriber order entry systems (CPOE).

Most of the studies included in the systematic review were from the USA and their focus was largely on adverse drug events or medication prescribing errors, and not specifically on drug allergy. In addition, few studies assessed the effectiveness of patient-held documentation strategies. The quality of the evidence from studies was generally very low. Research is therefore needed to determine which strategy or combination of strategies is most effective in reducing harm by minimising accidental re-exposure to a known drug allergen.

Population	All patients who receive drug treatment in the NHS (It is important to be able to distinguish patients who have no known allergies from those who have had a suspected or proven allergic reaction to a drug.)
Intervention	Intervention A: Electronic health records with features specifically allocated for drug allergy detection and alerts Intervention B: Patient-held, structured documentation of drug allergy (for example, a letter, email, form, card)
Comparator(s)	Comparator A: Electronic health records without features specifically allocated for drug allergy detection and alerts Comparator B: Patient-held, wearable form of drug allergy alert (for example, bracelet, necklace) that does not contain structured and detailed record of drug N.B. The emphasis of this research recommendation is in a 'structured' format of documentation. It would not be appropriate to select 'standard care' for the comparators as it is presently not possible to define this term. Firstly, this is due to general lack of documentations specifically on drug

	allergies. The problem lies in the fact that any record related to drug allergies is often absorbed by the more generalised term of 'adverse drug reactions'. Secondly, the definition of 'standard care' is changing as the NHS is currently transitioning towards electronic health record systems from the more traditional paper records. The distinction of the two comparisons is where the documentation is held: one that is held in hospitals and another held by patients. The second comparison aims to assess whether a structured form of documentation held by patients is more effective in preventing the patient from being re-exposed to drug allergens than a non-structured documentation currently worn by some patients.
Outcome	Rate of re-exposure to drug known to cause allergy Extent of morbidity as a result of re-exposure to the drug allergen Prevalence of patients with no record of drug allergy status Quality of life Costs associated with treating patients re-exposed to known drug allergens
Study Design	Systematic review Randomised controlled trial Prospective cohort studies
Timeframe	NHS England has recently allocated technology funds to 58 hospital trusts in England to introduce electronic prescribing systems over the next 3 years. This offers a unique opportunity to undertake higher quality research (for example, an RCT) to determine the effectiveness of this and other documentation strategies held by healthcare professionals and patients.
Importance to patients or the population	Patients with known drug allergies expect that healthcare providers have effective systems to protect them from accidental re-exposure from known drug allergens. Patient safety incident reports and research indicate that the current systems do not provide effective safeguards to manage this risk.
Relevance to NICE guidance	Having evidence indicating which documentation strategy or combination of strategies will minimise the risk of accidental re-exposure to known drug allergens is of high importance as it is essential to inform future updates of the key recommendations in the guideline.
Relevance to the NHS	It is of the highest importance to the NHS that there are strategies in place to deliver safe healthcare. There are reputational, financial and operational benefits to implementation of systems that minimise serious harms from known drug allergy.
National priorities	The current NHS Outcomes Framework 2013–2014 identifies minimising serious harms arising from unsafe use of medicines as a priority. To achieve this objective, it is important to minimise incidence of accidental re-exposures to known drug allergens.
Current evidence base	The studies included in this systematic review showed that a wide range of documentation strategies exist. However, most of the studies were conducted in the US and the data may not be applicable to the UK. Medicine management systems operating in the UK differ significantly from those in other countries. Most of the studies directed their focus on adverse drug events and medication prescribing errors. There is a limited amount of data specifically on drug allergy. An ideal study should have its focus on prevention of re-exposure to drug allergens. Overall, the current evidence base is of very low quality.
Equality	There are no equality issues arising from this research question. All patients in whatever healthcare setting should be protected from accidental re-exposure to known drug allergens.

Feasibility	The proposed research can be carried out within a realistic timescale of between 1 to 2 years. There are no ethical or sample size issues. NHS England has recently allocated technology funds to 58 hospital trusts in England to introduce electronic prescribing systems over the next 3 years. This offers a unique opportunity to undertake high quality research studies to determine the effectiveness of electronic prescribing systems and other forms of documentations held by healthcare professionals and patients.
Other comments	This is a very important research question for patient safety. Research into effective documentation strategies for drug allergy in all healthcare sectors is long overdue.

M.4 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?

Why is this important?

There are 5.4 million people with asthma in the UK, 1–5% of whom are unable to take non-selective NSAIDs without developing a severe and sometimes life-threatening asthma attack. In addition, 0.1–1% of the general population report allergic reactions to NSAIDs with symptoms ranging from urticaria and angioedema to anaphylaxis. NSAIDs are extremely widely used, are available over the counter and are present within many compound preparations, for example cold and flu remedies. People who are allergic to NSAIDs are therefore at risk of inadvertent exposure and this presents a significant public health issue.

Commonly encountered NSAIDs such as aspirin, ibuprofen, diclofenac and naproxen are non-selective COX-2 inhibitors which block the enzymatic effects of both cyclooxygenase 1 (COX-1) and COX-2. More recently introduced NSAIDs include a group which are selective inhibitors of the COX-2 isoform alone. Studies have shown that the allergic response to NSAIDs is mediated through inhibition of COX-1 and therefore the majority of people with a history of allergic reactions to non-selective NSAIDs are able to tolerate selective COX-2 inhibitors. However, the same studies have also reported that a small proportion of these people also react adversely to selective COX-2 inhibitors. This group has not been properly characterised and therefore it is not possible to predict who should be offered a selective COX-2 inhibitor without undertaking specialist drug allergy investigations. This clinical guideline recommends that people with a history of mild reactions should be offered a selective COX-2 inhibitor but that all those with severe or asthmatic reactions be referred to specialist drug allergy services for investigation before they can be offered treatment.

Well-designed, appropriately powered, controlled studies characterising people with a history of severe and asthmatic reactions to non-selective NSAIDs may enable them to have treatment with an anti-inflammatory without specialist drug allergy investigation.

Population	• Adults with a history of severe allergic reaction to NSAIDs stratified into: • Adult patients with a history of anaphylaxis from NSAIDs • Adult patients with eosinophilic asthma and nasal polyposis who have experienced an exacerbation of asthma from NSAIDs Confirmed by a placebo controlled challenge of their allergy to NSAIDs

Intervention	Challenge with a selective COX-2 inhibitor
Comparator(s)	• Challenge with a less selective COX-2 inhibitor (meloxicam) • Challenge with a placebo • Challenge with a selective COX-2 inhibitor versus a different selective COX-2 inhibitor and take for seven (7) days to monitor for longer term side effects Comparison with meloxicam, a preferential but less selective COX-2 inhibitor in addition to placebo would help to define differences in degree of intolerance to COX-1 inhibitors within each patient subgroup.
Outcome	The frequency and severity of allergic reactions to a selective COX-2 inhibitor in each of the two patients groups Cost comparison if NHS if referral was not needed and cost of alternative less effective analgesics with greater side effects, for example opiates which do not have anti-inflammatory activity or corticosteroids which have anti-inflammatory actions. Loss to follow-up. Adverse drug reactions other than allergic reactions
Study Design	Details of methodology would need careful consideration but a placebo controlled cross over design is likely to be appropriate with appropriate wash-out periods between different types of selective COX-2 inhibitors.
Timeframe	The study would require several follow-up visits after challenge tests as well as longer term 6 months and 1 year follow-up to assess the uptake of selective COX-2 inhibitors.
Importance to patients or the population	Ability to take an effective anti-inflammatory and analgesic without the delay of undergoing referral to specialist drug allergy services.
Relevance to NICE guidance	Current NICE guidance recommends referral of such patients for specialist drug allergy referral. If the study could identify which groups do not need specialist referral then this would reduce delay in treatment and save NHS costs. The results would inform the key recommendations to future NICE guidance.
Relevance to the NHS	This group of patients is at potential risk of fatal anaphylaxis when taking NSAIDs which are available over the counter. A readily available effective alternative treatment which could be recommended in primary care would reduce costs, improve patient safety and reduce morbidity from inappropriate prescribing.
National priorities	Establishes the principle of safety not for a single drug but for a class of drugs with a different mechanism of action in a selected group of patients who have very limited therapeutic options because they cannot take NSAIDs.
Current evidence base	See systematic literature review on the subject that identified current studies to be of poor quality and not suited to answering the question adequately.
Equality	Patients with multiple co-morbidities or the elderly who are considered too frail to undergo specialist investigation of drug allergy would benefit particularly.
Feasibility	A power calculation would be needed to estimate sample size and that would determine cost and timescale.
Other comments	N/A

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