Appendix C: Clinical review protocols

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