National Institute for Health and Clinical Excellence

Issue date: December 2011

Anaphylaxis

Assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode

NICE clinical guideline 134
Developed by the Centre for Clinical Practice at NICE

NICE clinical guideline 134

Anaphylaxis

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- The NICE guideline – all the recommendations.
- The NICE pathway – a set of online diagrams that brings together all NICE guidance and support tools.
- 'Understanding NICE guidance' – a summary for patients and carers.
- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on.

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This guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summary of product characteristics of any drugs they are considering.

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Contents

Appendices C, D, E, F and G are in separate files.

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Introduction

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by rapidly developing, life-threatening problems involving: the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia). In most cases, there are associated skin and mucosal changes[1].

In emergency departments a person who presents with the signs and symptoms listed above may be classified as having a 'severe allergic' reaction rather than an 'anaphylactic' reaction. Throughout this guideline, anyone who presents with such signs and symptoms is classed as experiencing a 'suspected anaphylactic reaction', and should be diagnosed as having 'suspected anaphylaxis'.

People who have had a mild or moderate allergic reaction are at risk of, and may subsequently present with, suspected anaphylaxis. Certain groups may be at higher risk, either because of an existing comorbidity (for example asthma) or because they are more likely to be exposed to the same allergen again (for example people with venom allergies or reactions to specific food triggers). These groups were not included within the scope of this guideline, which is specific to those who have received emergency treatment for suspected anaphylaxis.

Anaphylaxis may be an allergic response that is immunologically mediated, or a non-immunologically mediated response, or idiopathic. Certain foods, insect venoms, some drugs and latex are common precipitants of immunoglobulin E (IgE)-mediated allergic anaphylaxis. Many drugs can also act through non-allergic mechanisms. A significant proportion of anaphylaxis is classified as idiopathic, in which there are significant clinical effects but no readily

[1] Resuscitation Council (UK) 2008. Emergency treatment of anaphylactic reactions. Guidelines for healthcare providers.

identifiable cause. The relative likelihood of the reaction being allergic, non-allergic or idiopathic varies considerably with age.

Food is a particularly common trigger in children, while medicinal products are much more common triggers in older people. In the UK it is estimated that 500,000 people have had a venom-induced anaphylactic reaction and 220,000 people up to the age of 44 have had a nut-induced anaphylactic reaction[2].

There is no overall figure for the frequency of anaphylaxis from all causes in the UK. Because anaphylaxis presents mainly in accident and emergency departments and outpatient settings, few estimates of prevalence are available from NHS sources. Anaphylaxis may not be recorded, or may be misdiagnosed as something else, for example, asthma. It may also be recorded by cause, such as food allergy, rather than as an anaphylactic reaction.

Available UK estimates suggest that approximately 1 in 1333 of the population of England has experienced anaphylaxis at some point in their lives[3]. There are approximately 20 deaths from anaphylaxis reported each year in the UK, with around half the deaths being iatrogenic[4], although this may be an underestimate.

After an acute anaphylactic reaction, it is believed that many people do not receive optimal management of their condition. One reason for this is healthcare professionals' lack of understanding when making a diagnosis, for example failing to differentiate anaphylaxis from less severe histamine-releasing reactions or from other conditions that mimic some or all of its clinical features. Another reason is a lack of understanding of when or where to refer patients. This can affect the likelihood of the person receiving a

[2] Ewan PW for the British Society for Allergy and Clinical Immunology (2006) The nature and extent of allergy in the United Kingdom. A report to the Department of Health Review of Allergy Services.
[3] Stewart AG, Ewan PW (1996) The incidence, aetiology and management of anaphylaxis presenting to an accident and emergency department. Quarterly Journal of Medicine 89 (11): 859–64
[4] Pumphrey RS (2000) Lessons for management of anaphylaxis from a study of fatal reactions. Clinical and Experimental Allergy 30(8): 1144–50

definitive diagnosis, which can lead to anxiety, inappropriate management and recurrent reactions. It can also lead to avoidable costs for the NHS and increase the need for acute care.

Drug recommendations

The guideline does not make recommendations on drug dosage; prescribers should refer to the 'British national formulary' for this information. The guideline also assumes that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Who this guideline is for

This document is for staff in primary, secondary and tertiary settings who care for people with suspected anaphylaxis.

Patient-centred care

This guideline offers best practice advice on the care of adults, young people and children following emergency treatment for suspected anaphylaxis. For the purpose of this guideline all patients under 16 are classed as children. Those aged 16 and 17 are classed as young people and those aged 18 and over as adults.

Treatment and care should take into account patients' needs and preferences. People with suspected anaphylaxis should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent (available from www.dh.gov.uk/consent) and the code of practice that accompanies the Mental Capacity Act (summary available from www.dh.gov.uk/en/SocialCare/Deliveringsocialcare/MentalCapacity). In Wales, healthcare professionals should follow advice on consent from the Welsh Government (available from www.wales.nhs.uk/consent).

If the patient is under 16, healthcare professionals should follow the guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk/consent).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

Families and carers should be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with suspected anaphylaxis. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1 Recommendations

1.1 List of all recommendations

1.1.1 Document the acute clinical features of the suspected anaphylactic reaction (rapidly developing, life-threatening problems involving the airway [pharyngeal or laryngeal oedema] and/or breathing [bronchospasm with tachypnoea] and/or circulation [hypotension and/or tachycardia] and, in most cases, associated skin and mucosal changes).

1.1.2 Record the time of onset of the reaction.

1.1.3 Record the circumstances immediately before the onset of symptoms to help to identify the possible trigger.

1.1.4 After a suspected anaphylactic reaction in adults or young people aged 16 years or older, take timed blood samples for mast cell tryptase testing as follows:

- a sample as soon as possible after emergency treatment has started
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

1.1.5 After a suspected anaphylactic reaction in children younger than 16 years, consider taking blood samples for mast cell tryptase testing as follows if the cause is thought to be venom-related, drug-related or idiopathic:

- a sample as soon as possible after emergency treatment has started
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

1.1.6 Inform the person (or, as appropriate, their parent and/or carer) that a blood sample may be required at follow-up with the specialist allergy service to measure baseline mast cell tryptase.

1.1.7 Adults and young people aged 16 years or older who have had emergency treatment for suspected anaphylaxis should be observed for 6–12 hours from the onset of symptoms, depending on their response to emergency treatment. In people with reactions that are controlled promptly and easily, a shorter observation period may be considered provided that they receive appropriate post-reaction care prior to discharge.

1.1.8 Children younger than 16 years who have had emergency treatment for suspected anaphylaxis should be admitted to hospital under the care of a paediatric medical team.

1.1.9 After emergency treatment for suspected anaphylaxis, offer people a referral to a specialist allergy service (age-appropriate where possible) consisting of healthcare professionals with the skills and competencies necessary to accurately investigate, diagnose, monitor and provide ongoing management of, and patient education about, suspected anaphylaxis.

1.1.10 After emergency treatment for suspected anaphylaxis, offer people (or, as appropriate, their parent and/or carer) an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment.

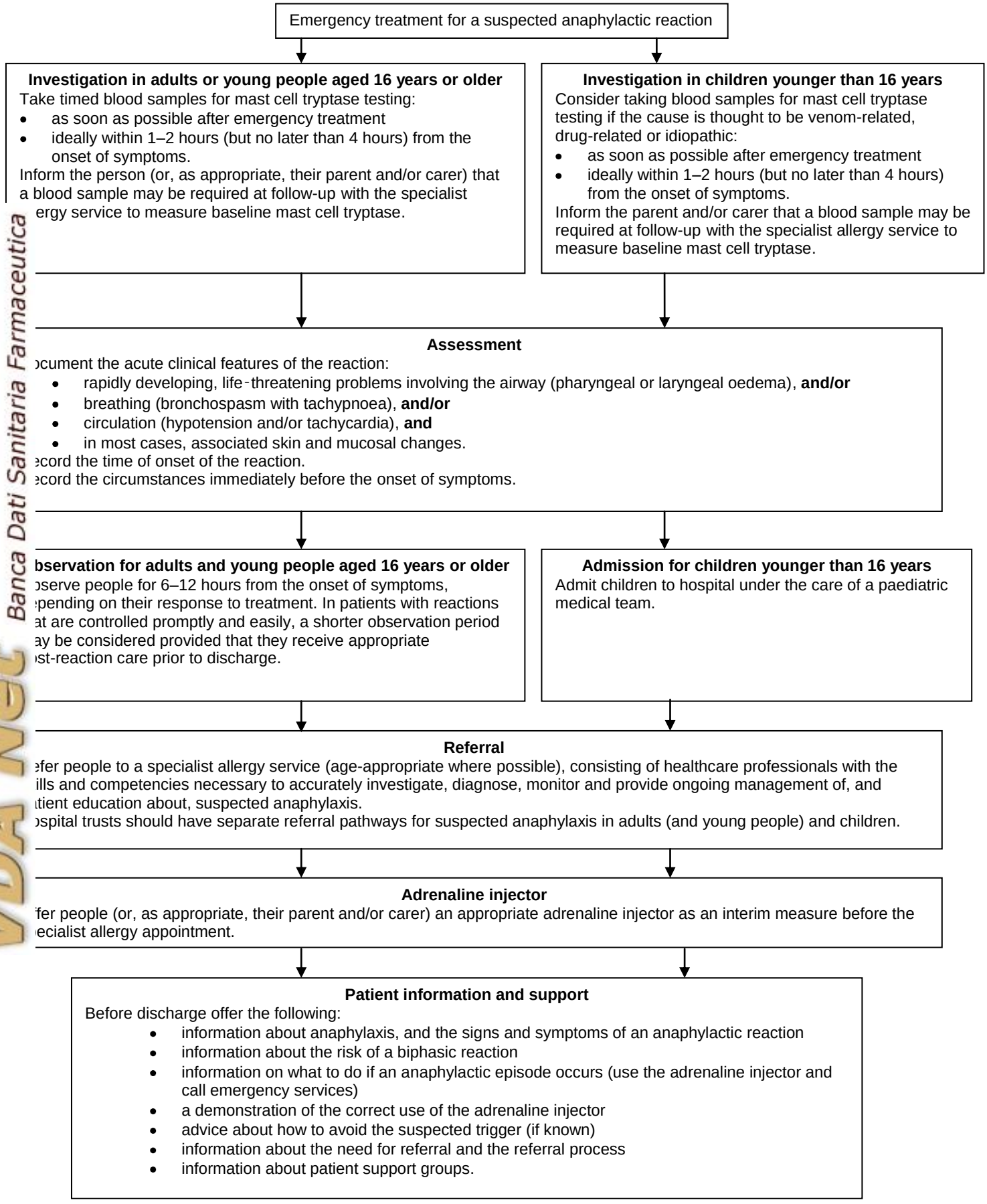
1.1.11 Before discharge a healthcare professional with the appropriate skills and competencies should offer people (or, as appropriate, their parent and/or carer) the following:

- information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction
- information about the risk of a biphasic reaction

- information on what to do if an anaphylactic reaction occurs (use the adrenaline injector and call emergency services)
- a demonstration of the correct use of the adrenaline injector and when to use it
- advice about how to avoid the suspected trigger (if known)
- information about the need for referral to a specialist allergy service and the referral process
- information about patient support groups.

1.1.12 Each hospital trust providing emergency treatment for suspected anaphylaxis should have separate referral pathways for suspected anaphylaxis in adults (and young people) and children.

2 Care pathway



3 Evidence review and recommendations

A systematic review of clinical effectiveness (sections 3.1.2, 3.2.2, 3.4.2 and 3.5.2) was completed by NICE. For details of how this guideline was developed, see appendix D. A technical assessment report, which comprised of a systematic review of clinical and cost effectiveness with additional health-economic modelling (sections 3.3.2 and 3.3.4) was commissioned by NICE from Kleijnen Systematic Reviews Ltd, based in York, England. For full details of the technical assessment report, see appendices F and G. For the full evidence tables please see appendix E.

3.1 Use and timing of mast cell tryptase testing in the anaphylaxis diagnostic pathway

3.1.1 Review question

Should mast cell tryptase testing be performed in patients with suspected anaphylaxis? If so, what is the optimal timing for testing?

3.1.2 Evidence review

A total of 642 articles were found by systematic searches. Full text was ordered for 67 articles based on the title and abstract. Of these, 17 papers (Brown et al. 2004; Dybendal et al. 2003; Enrique et al. 1999; Fisher and Baldo 1998; Fisher et al. 2009; Kanthawatana et al. 1999; Laroche et al. 1991; Laroche et al. 1992a; Laroche et al. 1992b; Laroche et al. 1998; Malinovsky et al. 2008; Mertes et al. 2003; Ordoqui et al. 1997; Schwartz et al. 1987; Schwartz et al. 1989; Schwartz et al. 1994; Stone et al. 2009) met the eligibility criteria and described the use or timing of mast cell tryptase testing to confirm an anaphylactic reaction.

Studies were included if they evaluated mast cell tryptase testing in adults and children who received emergency treatment for suspected anaphylaxis. Studies were excluded if they measured mast cell tryptase postmortem or baseline serum levels only (for the full review protocol and inclusion and exclusion criteria, see appendix D).

The Guideline Development Group (GDG) considered that further exclusion criteria should be applied. Studies that compared mast cell tryptase with other tests (for example skin-prick tests or in-vitro IgE tests) alone, without clinical assessment, were excluded because the results of these tests alone are not sufficient to diagnose anaphylaxis and were therefore inappropriate as reference standards.

The studies that met the eligibility criteria used a range of methods to measure mast cell tryptase. It was noted that most of the included studies on the timing of mast cell tryptase testing employed methods that are not currently used in the UK. However, the GDG's view was that the type of test used does not significantly impact upon an overall assessment of the timing of acute mast cell tryptase release.

Table 1 Studies excluded because the comparator did not include clinical assessment

Study	Comparison
Dybendal (2003)	SPT/IgE
Fisher (1998)	SPT/IgE
Fisher (2009)	SPT/IgE
Laroche (1992a)	SPT/IgE
Abbreviations: IgE, immunoglobulin E; SPT, skin-prick test.	

A total of 13 studies were included in the final review; 4 on the utility of mast cell tryptase testing (Brown et al. 2004; Enrique et al. 1999; Malinovsky et al. 2008; Mertes et al. 2003) and 9 on timing (Kanthawatana et al. 1999; Laroche et al. 1991; Laroche et al. 1992b; Laroche et al. 1998; Ordoqui et al. 1997; Schwartz et al 1987; Schwartz et al. 1989; Schwartz et al. 1994; Stone et al. 2009).

Table 2 Summary of included studies on the use of mast cell tryptase testing in the diagnosis of anaphylaxis

Study ID Test type	Mast cell tryptase threshold	Reference standard	Population	Study type	Experimentally induced or 'natural' presentation	Allergen (if single/ named allergen study)
Brown (2004) FEIA (UniCAP)	12.0 µg/l peak	Clinical diagnosis	Adults (assumed)	Cross-sectional prospective	Experimental challenge	Jack jumper ant
	9.0 µg/l peak	Clinical diagnosis				
	2.0 change	Clinical diagnosis				
Enrique (1999) FEIA (UniCAP)	13.50 ng/ml	Clinical criteria + immuno-allergic study	Adults	Cross-sectional prospective (assumed)	Natural	Various
	8.23 ng/ml	Clinical criteria + immuno-allergic study				
Malinovsky (2008) FEIA (UniCAP)	12 µg/l	Clinical assessment and immuno-allergic study	Adults and children	Cross-sectional prospective	Natural	Anaesthesia
	25 µg/l	Clinical assessment and immuno-allergic study				
	Not reported	Clinical assessment and immuno-allergic study				
Mertes (2003) FEIA (UniCAP)	25 µg/l	Clinical history, skin tests and/or specific IgE assay	Adults (assumed)	Cross-sectional retrospective	Natural	Anaesthesia
Abbreviations: IgE, immunoglobulin E; FEIA, fluoroenzymeimmunoassay.						

Table 3 Summary of included studies on the timing of mast cell tryptase testing in the diagnosis of anaphylaxis

Study ID Test type	Population	Study type	Experimentally induced or 'natural' presentation	Allergen (if single/named allergen study)
Kanthawatana (1999) ELISA	Adults	Case series	Natural	Various
Laroche (1991) RIA	Adults	Case–control	Natural	Anaesthesia and other drugs
Laroche (1992b) RIA	Adults (assumed)	Case series	Natural	Drugs (mostly anaesthesia)
Laroche (1998) RIA	Adults	Case–control	Natural	Contrast media
Ordoqui (1997) RIA	Adults (assumed)	Case series	Natural	Drugs
Schwartz (1987) ELISA	Adults (assumed)	Case series	Natural	Various
Schwartz (1989) ELISA	Adults (assumed)	Case series	Bee sting challenge (n = 3) or natural (n = 2)	Various
Schwartz (1994) ELISA	Adults (assumed)	Case–control	Experimental challenge	Venom
Stone (2009) ELISA	Adults and children	Case series	Natural	Various
Abbreviations: ELISA, enzyme-linked immunosorbent assay; RIA, radioimmunoassay.				

GRADE (Grading of Recommendations Assessment, Development and Evaluation; see appendix D for details of the methods used) was applied to the studies. A diagnostic accuracy study (usually designed as prospective) was initially regarded as high quality, a diagnostic accuracy study (based on usually retrospective data, and not by design) as moderate quality, and any other design as low quality. For the timing studies, all started as low quality (because of the lack of experimental design or attempts to minimise potential bias).

As part of the GRADE process, the GDG considered how results from diagnostic accuracy studies, in the context of anaphylaxis, can be interpreted, and the impact that this would have on the patient, their family and the NHS.

True positives

A correct diagnosis of anaphylaxis means that the person will receive the correct treatment, which will minimise the risk of future reactions.

False positives

A diagnosis of suspected anaphylaxis in a person who did not have an anaphylactic reaction has an impact on their quality of life, increases levels of anxiety, and involves the potential use of unnecessary adrenaline, together with associated risks and costs. Importantly, the true cause of the reaction is not identified or treated.

False negatives

People who have had an anaphylactic reaction but who have a diagnosis that is not considered to be anaphylaxis will not be referred for specialist assessment or management. They are at risk of potentially life-threatening future reactions because the condition is not managed optimally.

True negatives

If a correct diagnosis is not considered to be anaphylaxis, the impact is to reduce anxiety. In addition, there may be wider social implications, for example, a reduction in ‘blanket’ rules where children are unnecessarily banned from bringing certain foods into school.

The GDG therefore considered that the aim of any test should be to minimise false negatives because of the high risk of further anaphylactic reactions.

Table 4 GRADE profile 1: Use of mast cell tryptase testing in the diagnosis of anaphylaxis compared with clinical assessment

Study characteristics		Index and reference tests			Quality assessment					Summary of findings							
Study ID	**Study design**	**Index**	**Reference**	**N**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pre-test prob**	**TP (%)**	**FP (%)**	**FN (%)**	**TN (%)**	**Sens (95% CI)**	**Spec (95% CI)**	**Quality**
Mast cell tryptase low threshold at peak																	
Enrique (1999)	Cross-sectional	Mast cell tryptase (TH 8.23 ng/ml)	Clinical diagnosis + immunological tests	30	n	s[a]	s[b]	s[c]	n	0.57	13 (43)	1 (3)	4 (13)	12 (40)	76 (50–93)	92 (64–100)	Very low
Brown (2004)	Cross-sectional	Mast cell tryptase (TH 9.0 µg/l peak)	Clinical diagnosis alone	64						0.17	6 (9)	7 (11)	5 (8)	46 (72)	55 (22–83)	87 (75–95)	
Mast cell tryptase medium threshold at peak																	
Brown (2004)	Cross-sectional	Mast cell tryptase (TH 12.0 µg/l peak)	Clinical diagnosis alone	64	n	s[a]	s[b]	s[c]	n	0.17	4 (6)	6 (9)	7 (11)	47 (73)	36 (11–69)	89 (77–96)	Very low
Enrique (1999)	Cross-sectional	Mast cell tryptase (TH 13.50 ng/ml)	Clinical diagnosis + immunological tests	30						0.57	6 (20)	1 (3)	11 (37)	12 (40)	35 (14–62)	92 (64–100)	
Malinovsky (2008)	Cross-sectional	Mast cell tryptase (TH 12 µg/l)	Clinical diagnosis + immunological tests	31						0.71	14 (45)	1 (3)	8 (26)	8 (26)	64 (59–100)	89 (7–93)	

Mast cell tryptase high threshold at peak																	
Malinovsky (2008)	Cross-sectional	Mast cell tryptase (TH 25 µg/l)	Clinical diagnosis + immunological tests	31	n	s[a]	s[b]	s[c]	n	0.71	9 (29)	0 (0)	13 (42)	9 (29)	41 (21–64)	100 (66–100)	Very low
Mertes (2003)	Cross-sectional	Mast cell tryptase (TH 25 µg/l)	Clinical diagnosis + SPT +/or IgE	259						0.68	112 (43)	9 (3)	63 (24)	75 (29)	64 (56–71)	89 (81–95)	
Mast cell tryptase change from baseline																	
Brown (2004)	Cross-sectional	Mast cell tryptase (TH 2.0 µg/l change)	Clinical diagnosis alone	64	n	s[d]	s[b]	s[c]	n	0.17	8 (13)	5 (8)	3 (5)	48 (75)	73 (39–94)	91 (79–97)	Very low
Mast cell tryptase threshold not defined																	
Malinovsky (2008)	Cross-sectional	Mast cell tryptase (TH not reported)	Clinical diagnosis + immunological tests	7	n	s[d]	s[b]	n	n	0.60	39 (56)	0 (0)	3 (4)	28 (40)	93 (81–99)	100 (88–100)	Very low

[a] Results showed some inconsistency across studies (downgraded one level)

[b] Studies evaluated tests in experimentally induced reactions; or were single allergen studies so may not be representative of the guideline population (downgraded one level)

[c] Confidence intervals were wide (downgraded one level)

[d] Inconsistency was not assessable because there was only one study (downgraded one level)

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; n, not serious; prob, probability; s, serious; Sens, sensitivity; Spec, specificity; SPT, skin-prick test; TH, threshold; TN, true negative; TP, true positive.

Table 5 GRADE profile 2: Timing of mast cell tryptase testing in the diagnosis of anaphylaxis

Quality assessment						Summary of findings	Quality
No. of studies	**Study design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**		
Baseline assessment of mast cell tryptase							
9 Kanthawatana (1999) Laroche (1991) Laroche (1992b) Laroche (1998) Ordoqui (1997) Schwartz (1987) Schwartz (1989) Schwartz (1994) Stone (2009)	Observational	Not reported in included studies					Not applicable
Timing of peak mast cell tryptase							
7 Kanthawatana (1999) Laroche (1991) Ordoqui (1997) Schwartz (1987) Schwartz (1989) Schwartz (1994) Stone (2009)	Observational	n	s[a]	n	s[b]	Timing of peak levels ranged from 1 minute to 6 hours. Median reported in studies (excluding the biphasic peaks) was 30 minutes. Reported levels varied with median of 24 U/l (range 4.09–66.2). However, one study found no correlation between the timing of onset of symptoms and mast cell tryptase levels.	Very low

Quality assessment						Summary of findings	Quality
No. of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision		
End-point of elevated mast cell tryptase							
6 Laroche (1991) Laroche (1992b) Laroche (1998) Ordoqui (1997) Schwartz (1987) Schwartz (1989)	Observational	n	s[a]	n	s[b]	Reported $t_{1/2}$ was median 90 minutes (range 30–300 minutes). Levels usually returned to normal by 24 hours after onset of symptoms. One study reported normal levels (18 ng/ml) at 6 hours.	Very low

[a] Results showed some inconsistency across studies (downgraded one level)

[b] Results as reported did not allow any assessment of the level of imprecision (downgraded one level)

Abbreviations: n, not serious; s, serious; $t_{1/2}$, half-life; U/l, units per litre.

See appendix E for the evidence tables in full.

3.1.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

Use of mast cell tryptase testing in the diagnosis of anaphylaxis

3.1.3.1 No evidence on the clinical utility of mast cell tryptase testing in the diagnosis of anaphylaxis in children was identified.

Malinovsky (2008) included 1 child (participants' ages ranged from 8 years to 80 years, with a median of 43 years) within the study. However, data were not provided on the diagnostic accuracy of mast cell tryptase in children.

3.1.3.2 Very low-quality evidence from four observational studies including 384 patients showed that peak mast cell tryptase had a high specificity when compared with clinical assessment (range 87% to 100%, dependent on the threshold used). Sensitivity tended to be lower (range 35% to 93%, dependent on the threshold used).

Brown (2004) measured peak mast cell tryptase after an experimental jack jumper ant venom challenge in patients with a history of anaphylactic reactions, giving a sensitivity of 36% and specificity of 89% (threshold: 12.0 microgram/l). Enrique (1999) measured peak mast cell tryptase in patients presenting with suspected anaphylaxis from a number of causes, giving a sensitivity of 35% and specificity of 92% (threshold: 13.50 nanogram/ml). Malinovsky (2008) measured peak mast cell tryptase in patients presenting with suspected anaphylaxis from anaesthesia, giving a sensitivity of 64% and specificity of 89% (threshold: 12.0 nanogram/ml). Mertes (2003) measured peak mast cell tryptase in patients presenting with suspected anaphylaxis during anaesthesia, giving a sensitivity of 64% and specificity of 89% (threshold: 25 microgram/l).

3.1.3.3 Very low-quality evidence from one observational study of 64 patients showed that change in mast cell tryptase (from baseline to peak) had a sensitivity of 73% and specificity of 91% for the diagnosis of anaphylaxis when compared with a clinical diagnosis.

Brown (2004) evaluated the change from baseline after an experimental jack jumper ant venom challenge.

Timing of mast cell tryptase testing in the diagnosis of anaphylaxis

3.1.3.4 No evidence on the timing of mast cell tryptase testing in the diagnosis of anaphylaxis in children was identified.

Stone (2009) included children (participants' age ranged from 9 years to 99 years, with a median of 36 years); results were not reported separately for children.

3.1.3.5 No information on the optimal timing of baseline measurement of mast cell tryptase was identified.

3.1.3.6 Very low-quality evidence from seven observational studies including 178 patients showed that the timing of peak levels ranged from 1 minute to 6 hours (median 30 minutes). Reported levels varied with a median of 24 units per litre (range 4.09–66.2).

Laroche (1991), Ordoqui (1997), Schwartz (1989) and Schwartz (1994) assessed the timing of peak mast cell tryptase in anaphylactic reactions to anaesthesia, drugs and venom, while Kanthawatana (1999), Schwartz (1987) and Stone (2009) considered a range of allergens.

3.1.3.7 Very low-quality evidence from six observational studies including 147 patients showed that the half-life of tryptase ranged from 30 minutes to 300 minutes (median 90 minutes). Levels returned to normal by 24 hours after the onset of symptoms.

Laroche (1991), Laroche (1998), Ordoqui (1997) and Schwartz (1989) assessed the timing of the half-life of mast cell tryptase in anaphylactic reactions to anaesthesia, drugs and contrast media, while Laroche (1992b) and Schwartz (1987) considered a range of allergens.

3.1.4 Health economic modelling

A health economic analysis was not conducted for this question. The cost per patient per test is not straightforward to establish. The only data source

identified was from the University of Birmingham Clinical Immunology service handbook and price list, which quoted £14 (up to 28-day turnover). As the analysis of multiple blood samples may be encompassed in this cost, it appears to be a reasonable estimate with respect to the reference cost for immunology tests; £7 (lowest cost £4, highest £9, based on 2009–10 reference costs for DAP830 Immunology).

This suggests that mast cell tryptase testing represents a modest but non-negligible cost to the NHS. However, it is currently conducted as part of the management plan during follow-up at specialist allergy clinics. For this reason, the cost of mast cell tryptase testing is assumed to be incorporated in the cost of a visit to a specialist allergy service in the health economic model described in section 3.3.4. Conducting a separate analysis here would run the risk of double-counting.

3.1.5 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that the aim of any test for anaphylaxis should be to minimise false negatives because of the risk of future events. While the evidence on the mast cell tryptase test was inconsistent in the rates of true positives (sensitivity), the rate of false negatives (specificity) was low. As a result of the demonstrated low false negative rate and because the results from mast cell tryptase tests would normally be interpreted by an allergy specialist in conjunction with a clinical assessment, the GDG felt that the use of mast cell tryptase was warranted. The evidence suggested a median time of 30 minutes for the peak of mast cell tryptase, but that this could vary between 1 minute and 6 hours. It was noted that the peak had been reached in all but 2 patients within 2 hours. The half-life ranged from 30 minutes to 5 hours (median of 90 minutes). As a result, the GDG agreed that the timing of the first blood sample should be as soon as possible after the onset of symptoms as this would most likely capture the initial rise or peak of mast cell tryptase. However, as a result of the variation between individuals the GDG felt that an additional blood sample was needed. The aim of this second blood sample would be to better understand the pattern of tryptase release and breakdown, which would aid the clinical interpretation of the results of the first sample. It was felt that the most appropriate and practical time to take the second sample would be 1–2 hours after the onset of symptoms. Although the evidence showed that the half-life and peak had occurred after 5 or 6 hours in a few cases, the GDG felt that this was atypical. In the GDG's opinion tryptase would have peaked within 4 hours in the majority of cases. As a result they concluded that the second blood sample should not be taken any later than 4 hours after the onset of symptoms.

	As the evidence was predominantly in adults the GDG felt unable to make the same recommendation in children. The GDG's clinical experience suggested that false negatives are much higher in children, possibly as a result of most reactions being triggered by food, which does not always result in mast cell tryptase being elevated. Although there was no direct evidence to support the recommendation in children, the GDG felt that mast cell tryptase measurement was likely to be useful in children who present with idiopathic or suspected venom- or drug-induced anaphylaxis. It was also noted by the GDG that some patients had unexplained high levels of mast cell tryptase (for example, in mastocytosis), and therefore in order to interpret the results correctly it was important for a baseline sample to be taken. To aid the interpretation of the results it was agreed that this baseline sample would need to be taken at least 24 hours after the onset of symptoms, probably during specialist follow-up.
Trade-off between clinical benefits and harms	The GDG considered that although the evidence showed that there could be a risk of false positives with mast cell tryptase measurement (as the sensitivity of the tests reported in the studies varied considerably), this was an acceptable risk as the results would be interpreted by a specialist in conjunction with a clinical assessment.
Economic considerations	The recommendation should result in the test being conducted early (at emergency units) with a cost-neutral impact to the NHS, and an increased utility to the patient.
Quality of evidence	In addition to the very low quality of the evidence, the studies included a mixed population with a variety of causes of anaphylaxis and this could affect the study results (for example, suspected anaphylaxis in anaesthesia could be caused by technical anaesthetic or surgical problems).
Other considerations	Despite the very low quality evidence in diverse populations, the GDG considered mast cell tryptase testing to be justified in aiding specialist assessment. The pattern of mast cell tryptase levels after anaphylaxis is consistent with the GDG's clinical experience so the GDG also considered the use of the repeated mast cell tryptase measurements to be justified.

3.1.6 Recommendations and research recommendations for the use and timing of mast cell tryptase testing in the anaphylaxis diagnostic pathway

Recommendations

Recommendation 1.1.4

After a suspected anaphylactic reaction in adults or young people aged 16 years or older, take timed blood samples for mast cell tryptase testing as follows:

- a sample as soon as possible after emergency treatment has started
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

Recommendation 1.1.5

After a suspected anaphylactic reaction in children younger than 16 years, consider taking blood samples for mast cell tryptase testing as follows if the cause is thought to be venom-related, drug-related or idiopathic:

- a sample as soon as possible after emergency treatment has started
- a second sample ideally within 1–2 hours (but no later than 4 hours) from the onset of symptoms.

Recommendation 1.1.6

Inform the person (or, as appropriate, their parent and/or carer) that a blood sample may be required at follow-up with the specialist allergy service to measure baseline mast cell tryptase.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B1

Aside from mast cell tryptase, which other chemical inflammatory mediators offer potential as indicators of anaphylaxis?

3.2 Duration of observation after a suspected anaphylactic reaction

3.2.1 Review question

Should people be observed after an anaphylactic reaction? And if so, for how long?

3.2.2 Evidence review

A total of 1096 articles were found by systematic searches. Full text was ordered for 73 articles based on the title and abstract. Of these, no studies assessed the effectiveness of observation or the length of time that any observation period should last (for the full review protocol and inclusion and exclusion criteria, see appendix D).

As a result of the lack of any relevant studies, 15 studies (Brady et al. 1996; Brazil et al. 1998; De Swert et al. 2008; Douglas et al. 1994; Ellis et al. 2007; Järvinen et al. 2009; Jirapongsananuruk et al. 2007; Lee et al. 2000; Mehr et al. 2009; Poachanukoon et al. 2006; Sampson et al. 1992; Scranton et al. 2009; Smit et al. 2005; Stark et al. 1986; Yang et al. 2008) on the rates and timing of biphasic reactions in those treated for a suspected anaphylactic reaction were considered as 'indirect' evidence and were presented to the GDG. Biphasic reactions were defined as those reactions that occurred following resolution of the index reaction symptoms, but without further exposure to the suspected allergen.

It was not possible to use GRADE to evaluate the quality of the studies because the evidence considered did not fit the GRADE framework of the original specified question (that is, studies comparing observation with no observation or varying times for observation). However, the overall low quality of the 'indirect' evidence was presented to the GDG to inform their discussions.

The GDG used the 'indirect' studies to prompt discussion on whether individuals should be observed following a suspected anaphylactic reaction and, if so, how long that period of observation should last. The recommendations were therefore based on the expertise, knowledge and experience of the GDG.

Table 6 Summary of study characteristics ('indirect' evidence)

Study ID	Study setting	Adults/children	N	Gender	Experimentally induced or 'natural' presentation	Allergen (if single/named allergen study)
Prospective studies						
De Swert (2008) Belgium Case series	Paediatric outpatient allergy clinic and two private practices (one in paediatrics and another in paediatric allergy) (includes some referrals)	Children (mean and median 6.9 y, 6 m to 14.8 y)	48	65% (31) male 35% (17) female	Natural	Various
Ellis (2007) Canada Cohort	Both outpatient (ED records) and inpatients	Both (mean 33 y, 11 m to 79 y)	134 (follow-up available for 103)	54% (56) male 47% (48) female	Natural	Various
Scranton (2009) USA Cohort	Patients treated with immunotherapy	Both (mean 33 y, 6 y to 76 y)	55	35% (19) male 65% (36) female	After immunotherapy	Immunotherapy (aeroallergen or venom)
Stark (1986) USA Cohort	Consecutive patients treated by one hospital's internal medicine house staff	Adult (mean 41.8 y,17 y to 71 y)	25	28% (7) male 72% (18) female	Mostly natural (one anti-venom)	Various
Retrospective studies						
Brady (1996) USA Case series	Out-of-hospital, ED, hospital records	Adults (mean age 30.2 y) (not clear if children included)	67	51% (34) male 49% (33) female	Natural	Various
Brazil (1998) UK Case series	Admitted patients at short-stay ward in A&E	Adults (16–81 y)	34	56% (19) male 44% (15) female	Natural	Various
Douglas (1994) USA Case series	Both outpatient and inpatient (reported separately)	Both (outpatient mean 36 y, 7 y to 69 y; inpatient mean 35 y, 6 m to 81 y)	94 (35 outpatient, 59 inpatient)	Outpatient: 34% (12) male, 66% (23) female Inpatient: 71% (42) male, 29% (17) female	Natural	Various

Study ID	Study setting	Adults/children	N	Gender	Experimentally induced or 'natural' presentation	Allergen (if single/named allergen study)
Järvinen (2009) USA Case series	Patients tested with oral food challenge at hospital	Children (median 6 y, 1.25 y to 18 y)	50	60% (30) male 40% (20) female	Oral food challenge	Various foods
Jirapongsananuruk (2007) Thailand Case series	Inpatients	Both (mean 24 y, 2.8 m to 81.3 y)	101	52% (53) male 48% (48) female	Most natural (some immunotherapy)	Various
Lee (2000) USA Case series	Inpatients	Children (median 8 y, 6 m to 21 y)	106	61% (66) male 39% (42) female	Natural	Various
Mehr (2009) Australia Case series	Presenting at the ED and admitted into hospital for > 6 h	Children (median 2.5 y, 0.2 y to 18.8 y)	104	60% (62) male 40% (42) female	Natural	Various
Poachanukoon (2006) Thailand Case series	Outpatient (ED records)	Both (median 26 y, 1 m to 65 y)	64	53% (34) male 47% (30) female	Natural	Various
Sampson (1992) USA Cross-sectional	Various	Children (mean 12 y, 2 y to 17 y)	13	23% (3) male 77% (10) female	Natural	Food
Smit (2005) Hong Kong Case series	Patients presenting to ED resuscitation room	Both (median 28 y, 1 y to 91 y)	282	59% (167) male 41% (115) female	Natural	Various
Yang (2008) Korea Case series	Inpatients and outpatients at one centre	Both (mean 40 y, 5 y to 76 y)	138	54% (74) male 46% (64) female	Natural	Various
Abbreviations: A&E, accident and emergency; ED, emergency department; h, hour(s); m, month(s); y, year(s).						

Table 7 Summary of study results ('indirect' evidence)

Study ID	Anaphylaxis definition	Rate biphasic	Characteristics of biphasic reaction	Length of follow-up	Time of occurrence of biphasic reaction (h)		Other results/comments
					Mean/median	Range	
Prospective studies							
De Swert (2008)	Serious reaction with rapid onset of symptoms and/or involving two organ systems	3% (2/64)	Not clear	Not described	Not reported	30 min or 4 h after symptom resolution	Not reported
Ellis (2007)	Serious reaction with rapid onset of symptoms and/or involving two organ systems	19% (20/103)	Had to meet same definition as index reaction	Patients contacted 72 h after ED visit (mean ED observation time: 3.8 h)	10 (mean) after original reaction (unclear if from index reaction or symptom resolution)	2 to 38	40% (8) occurred more than 10 h later; 20% (4) occurred after 20 h (most within 22 h, but one at 38 h)
Scranton (2009)	Life-threatening (not otherwise described); assessed on 31-symptom score for five body systems (+ requiring adrenaline)	23% (14/60)	Any reaction (same scoring system used)	In-hospital: 1 to 2 h after last dose of adrenaline After discharge: patients contacted after 24 hours	5.5 (median) (unclear if from index reaction or symptom resolution)	2 to 24	Not reported
Stark (1986)	Based on two criteria (but both IgE and non-IgE-mediated)	20% (5/25)	Not clear	Observation for 12 h, or (if symptoms persisted beyond 12 h) until the reaction ceased, or until death	Not reported	Between 1 and 8 after symptom resolution of index reaction	Not reported
Retrospective studies							
Brady (1996)	Multi-system reaction involving ≥ two organ systems	3% (2/67)	Urticaria (but still went to and treated at ED)	Biphasic: 4 h to 7 h, 14 with uniphasic reactions that were admitted: mean 63 h Others: not reported	Not reported	26 and 40 after ED visit (not clear if from start of initial visit or after discharge)	Second reaction was relatively minor
Brazil (1998)	One or more system involved	18% (6/34)	Symptoms requiring adrenaline	Not described	Not reported	4.5 to 29.5 interval until development of biphasic reaction (unclear exactly when interval starts, that is, index reaction or symptom resolution)	All but one occurred within 24 h

Study ID	Anaphylaxis definition	Rate biphasic	Characteristics of biphasic reaction	Length of follow-up	Time of occurrence of biphasic reaction (h)		Other results/comments
					Mean/median	Range	
Douglas (1994)	One or more system involved	5% (2/44) (outpatient) 7% (4/59) (inpatient)	Three had only urticaria, one only angioedema and rhinitis, one tongue swelling and wheezing only	Outpatient: contact by nurse within 12 h to 24 h Inpatient: not described	Outpatient: 22 to 24 and 6 to 8 Inpatient: 1, 24, 24 and 72		Not reported
Järvinen (2009)	Multi-system reaction involving ≥ two organ systems	2% (1/50)	Not clear	Not described	1	Not reported	Not reported
Jirapongsananuruk (2007)	One symptom of generalised mediator release and one system affected.	7% (4/54) of children 2% (1/47) of adults	Not clear	Not described	Not reported	Not reported	Not reported
Lee (2000)	Acute reaction involving at least two body systems	6% (6/105)	Worsening of symptoms after index symptom resolution requiring new therapy	When significant reaction (requiring oxygen, vasopressors, intubation, subcutaneous adrenaline, unscheduled bronchodilator treatments), observed for 24 h (otherwise, not described)	Not reported	1.3 to 28.4 after symptom resolution of index reaction	All but one had occurred within 12 h
Mehr (2009)	Multi-system reaction involving respiratory/CV system and another organ system	5% (5/109)	Same	Not described	8.8 (median) from onset of index reaction	1.3 to 20.5	Not reported
Poachanukoon (2006)	One symptom of generalised mediator release and one system affected	15% (8/52)	Not clear	Not described	Not reported	Not reported	Not reported
Sampson (1992)	Only near-fatal or fatal cases included	Not reported	Not clear	Not described	Not reported	1 to 2	Not reported

Study ID	Anaphylaxis definition	Rate biphasic	Characteristics of biphasic reaction	Length of follow-up	Time of occurrence of biphasic reaction (h)		Other results/comments
					Mean/median	Range	
Smit (2005)	Both IgE-mediated and non-IgE-mediated systematic immune response	5% (15/282)	Any reaction occurring after symptom resolution	Median 10.6 h spent in observation ward (kept in ED observation ward if expected to be discharged within 12 to 24 h but follow-up protocol length not described)	8 (mean) from treatment of index reaction	1 to 23	Nine occurred more than 8 h after initial presentation and six of these 8 h after initial treatment
Yang (2008)	One of a number of criteria (including reduced blood pressure alone)	2% (3/138)	Not clear	Not described	Not reported	Not reported	Not reported
Abbreviations: CV, cardiovascular; ED, emergency department; h, hour(s); IgE, immunoglobulin E.							

See appendix E for the evidence tables in full.

3.2.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

3.2.3.1 No evidence on the effectiveness of observing people after a suspected anaphylactic reaction was identified.

3.2.3.2 No evidence on for how long people should be observed after a suspected anaphylactic reaction was identified.

3.2.4 Health economic modelling

This question was not considered an economic priority, due to lack of evidence. The GDG felt that, because the recommendation did not represent a major departure from current common practice, the likely cost impact could be assumed to be relatively small. It is acknowledged that health economic modelling could potentially provide a useful exploration of the trade-offs between cost, benefit and safety in this area. However, such an analysis would only become possible on the basis of substantial additional evidence. If data such as those specified in the research recommendations (see section 3.1.6) become available in future, consideration should be given to conducting economic evaluation of this question in any update of this guideline.

3.2.5 Evidence to recommendations

Relative value of different outcomes	The GDG agreed that biphasic reactions are a concern. The GDG noted that the rates reported in some of the studies were higher, in their experience, than those within the UK, but the reason for this was unclear. Some of the variation may have been due to incorrect reporting or differing criteria being applied to the biphasic reaction. However, because there is a risk of a biphasic reaction in those treated for suspected anaphylaxis the GDG agreed that some period of observation is necessary. The GDG considered the mixed evidence on whether specific patients are at risk of a biphasic reaction. The studies were relatively small and often inconsistent in demonstrating whether particular factors predicted a biphasic reaction. It was therefore difficult to recommend that particular groups be observed for longer. However, the GDG agreed that there was some evidence to suggest that the intensity of the treatment needed to address the index reaction might be predictive of a biphasic reaction. While not conclusive, the GDG felt that these factors should be taken into consideration when deciding for how long to observe a patient. It was felt that shorter observation periods could be

	warranted in those who seek and respond quickly to treatment. The GDG noted that the timing of the biphasic reactions varied greatly across the studies, with some reactions occurring more than 20 hours after the initial reaction. The GDG agreed that in their experience 8 hours would be likely to capture around 60% of cases. While taking into account the factors above, the GDG decided that patients should be observed over a period of 6–12 hours. This would capture the majority of biphasic reactions but still allow the clinician some flexibility for those patients in whom reactions were controlled promptly and easily. The GDG noted that this period of observation was not a distinct period of time, but would run alongside other activities, such as recovery from the initial treatment and the delivery of patient education prior to discharge. The GDG agreed that children (those younger than 16 years) should be treated differently to young people (aged 16 years or older) and adults. For many children and their parents and/or carers a suspected anaphylactic reaction is a traumatic experience and will raise many different issues. The GDG felt that it was important for children and their parents or carers to receive the appropriate care (for example, paediatric assessment, counselling, education) following emergency treatment. Therefore they decided that all children should be admitted to hospital following emergency treatment, to be cared for by a paediatric medical team.
Trade-off between clinical benefits and harms	Although there is a risk associated with discharging some patients early, the GDG felt that, due to the costs associated with observation and a reduction in the risk of a biphasic reaction as time went on, it was not feasible to recommend that all patients be observed for a period of days.
Economic considerations	Although no formal analysis was undertaken, the GDG was aware that timely discharge would minimise unnecessary resource use. The available data were considered insufficient to enable formal economic analysis of the question.
Quality of evidence	No direct evidence was identified. The GDG used ‘indirect’ studies to prompt discussion. The overall low quality of the ‘indirect’ evidence was noted by the GDG during their discussions.
Other considerations	It was acknowledged by the GDG that the recommendations were based, to large extent, on their expertise, knowledge and experience.

3.2.6 Recommendations and research recommendations for duration of observation after a suspected anaphylactic reaction

Recommendations

Recommendation 1.1.7

Adults and young people aged 16 years or older who have had emergency treatment for suspected anaphylaxis should be observed for 6–12 hours from the onset of symptoms, depending on their response to emergency treatment. In patients with reactions that are controlled promptly and easily, a shorter observation period may be considered provided that they receive appropriate post-reaction care prior to discharge.

Recommendation 1.1.8

Children younger than 16 years who have had emergency treatment for suspected anaphylaxis should be admitted to hospital under the care of a paediatric medical team.

Research recommendations

See appendix B for full details of research recommendations.

Research recommendation B2

What are the frequency, timing, severity and predictors of biphasic reactions in people who have received emergency treatment for anaphylaxis?

Research recommendation B3

For how long should a person who has received emergency treatment for anaphylaxis be observed?

3.3 Assessment and the decision to refer after a suspected anaphylactic reaction

3.3.1 Review questions

a) What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

b) Who should be referred, when, and to where or whom?

c) Who should be given an emergency treatment plan and when should that include an adrenaline injector?

3.3.2 Evidence review

A total of 11,058 articles were found by systematic searches. After the screening of titles and abstracts, 107 references were excluded. A total of 97 papers were obtained and the full texts screened. However, 10 papers considered to be eligible for inclusion could not be retrieved from the British Library. A total of 5 studies were included (for a full list of included and excluded studies, see appendix G).

Studies were considered relevant if they assessed the risk of recurrence, or if they included clinical assessment, provision of adrenaline injectors, or information on when referral should occur in those who have received emergency treatment for a suspected anaphylactic reaction.

a) What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

No evidence was found that answered this review question. The recommendations were therefore based on the expertise, knowledge and experience of the GDG.

b) Who should be referred, when, and to where or whom?

Five studies addressed the area of 'Who is at high risk of recurrent anaphylactic reactions, and for whom would further anaphylactic reactions have a significant impact?' (Cianferoni 2004; Decker 2008; Mehl 2005; Múgica Garcia 2010; Mullins 2003).

It was not possible to use GRADE to evaluate the quality of the studies as none of the studies matched the GRADE framework. The studies were

reviewed and the quality established. The main themes from the evidence were extracted and presented to the GDG in the form of summary tables (see tables 8 and 9).

Table 8 Summary of included studies: risk of recurrent anaphylactic reactions

Study	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
Cianferoni (2004)	Observational retrospective	Low risk of bias but unclear how patients were selected.	Recurrence defined as the presence of another anaphylactic reaction: at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnoea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents. Defined risk factors for recurrence: history of atopic dermatitis, current urticaria/angioedema, history to sensitivity to 1 food allergen.	7 y (SD 1 y, range 5–8.6 y)	N/R
Decker (2008)	Observational prospective	Low risk of bias but no definition of recurrence given.	No details provided.	Mean 1.1 y (range 7 d –13 y)	N/R
Mehl (2005)	Observational retrospective	Medium risk of bias as no definition of recurrence was given. Role of funding source unclear.	Questionnaire covering demographic data, symptoms and physical findings of the reaction, place of occurrence, suspected allergen, diagnostic tests, treatment modalities such as use of drugs, route of application, and drug administering person, hospitalisation and prescribed emergency set after the reaction.	1 y (patients identified over a period of 12 m retrospectively)	Industry: InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany ('financial support')
Múgica Garcia (2010)	Observational retrospective	Medium risk of bias as only 58.7% of previous cohort was included and no details on age, gender, weight and ethnicity were reported.	Recurrence defined as any new reaction of anaphylaxis, irrespective of the cause of the first reaction and whether the recurrence was the same or different. The recurrence of the same subtype of anaphylaxis was considered when the same subtype of anaphylaxis (e.g. food, drugs, exercise) was responsible for both the first reaction and for the recurrence.	N/R	N/R
Mullins (2003)	Observational prospective	Low risk of bias but no definition of recurrence given.	Recurrence presented as proportion of patients relapsing. Rate of recurrence/100 patient-years of observation: calculated by dividing the cumulative length of observation by the number of recurrences involving that trigger.	2.2 y	N/R
Abbreviations: d, day(s); m, month(s); N/R, not reported; SD, standard deviation; y, year(s).					

Table 9 Findings of included studies: risk of recurrent anaphylactic reactions

Study	No. of patients	Patient characteristics	Results
Cianferoni (2004) Setting: primary care, Italy	46 (of 76 from a previous cohort study, re-evaluated after a mean of 7 years) Inclusion for previous study: patients with anaphylaxis referred to an allergy unit (Florence, Italy) who had at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnoea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents.	Diagnosed anaphylaxis. Mean age 14 y (SD 4.92, range 7–26 y). Age at first reaction: 5.8 y (SD 4.9, 1–18 y). 61% male. No details on weight and ethnicity. Aetiology: food 19.5% (9/46), exercise 4.4% (2/46), drug 2.2% (1/46), idiopathic 4.4% (2/46).	Risk of recurrence: 30% (14/46)
Decker (2008) Setting: primary care USA	211 (visiting an emergency department). Diagnosed anaphylaxis criteria from the National Institutes of Health/Food and Allergy and Anaphylaxis network.	Mean age: 29.3 years (SD 18.2). 44.1% male. No further details.	Second event in 45/211 (21.3%). Median time of presentation: 395 days (range 7 d–13 y). Third event in 11/211 (5.2%). Risk of recurrence higher in women (relative risk 2.14, 95% confidence interval 1.17 to 3.9). No difference in age (p = 0.535) or race (p = 0.743) for a subsequent event.
Mehl (2005) Setting: primary care Germany	103 children (< 12 y) Inclusion: reported accidental anaphylactic reactions occurring during 12 months in infants and children below 12 years of age. Reports reviewed individually by two paediatric allergologists. Exclusion: reported cases excluded if the reported reaction was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not under the age of 12.	Median age 5 y (range 3 m to 12 y). 58% male. No details on weight and ethnicity. Causative allergen was known or strongly suspected in 95/103 (92%) of all patients. Overall: food 57% (59/103), insect sting 13% (13/103), SIT 12% (12/103), medication 6% (6/103), other 4% (4/103), unknown 8% (9/103). Foods only: 57% (59/103): peanut 20% (12/59), tree nut 20% (12/59), cow's milk 14% (8/59), fish 14% (8/59), hen's egg 7% (4/59), other 25% (15/59)	Recurrence: overall 27% (28/103), food-related 71% (20/28), insect sting 7% (2/28), SIT 7% (2/28), unknown 14.3% (4/28). Same allergen as reaction(s) in medical history: 50% (14/28). 'No significant difference was found for allergens looking only at severe reactions (grades III and IV)' (no data reported). Age differences: Food, 'patients significantly younger than the overall group' (mean 3.9 y, SD 3). SIT, 'significantly older' (mean 9.8 y, SD 1.9). Venom, 'patients significantly older' (mean 7.6 y, SD 3.2).
Múgica Garcia	933 (original cohort of 1590). Presented	Diagnosed anaphylaxis. Mainly urban community.	Overall risk 325/933 (34.8%).

Study	No. of patients	Patient characteristics	Results
(2010) Setting: primary care Spain	with anaphylaxis and were followed in allergy unit (no further details).	No details on age, gender, weight and ethnicity.	Same type as first reaction: latex 72.7%, food 38.8%, hymenoptera venom: 33.3%, unknown: 32.9%
Mullins (2003) Setting: primary care Australia	432 patients referred for evaluation of possible anaphylaxis to community-based specialist medical practice between February 1995 and July 2000.	Mean age 27.4 y (SD 19.5, range: 1–82). 48% male. No details on weight and ethnicity. First reaction during study course: 71%. First reaction before study: 29%.	130/304 (42.8%) have experienced 386 reactions of recurrent symptoms (median 2, range 0–18). Risk of overall recurrence: 57/100 patient-years. Risk of severe recurrence: 10/100 patient-years. Non-serious recurrences: 19.7 (85/432); had adrenaline: 1.2% (1/85). Serious recurrences: 10.4% (45/432); had adrenaline: 40% (18/45). No deaths. Risk factors for recurrence: exercise and idiopathic cause, female gender.
Abbreviations: d, day(s); m, month(s); SD, standard deviation; SIT, specific immunotherapy; y, year(s).			

See appendix E for the evidence tables in full.

c) Who should be given an emergency treatment plan and when should that include an adrenaline injector?

No evidence was found that answered this review question. The recommendations were therefore based on the expertise, knowledge and experience of the GDG.

3.3.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

a) What should be part of the review after a reaction to confirm a diagnosis of anaphylaxis and to guide referral?

3.3.3.1 No evidence was found on what should be part of the review after a reaction to confirm a suspected anaphylactic reaction and to guide referral.

b) Who should be referred, when, and to where or whom?

3.3.3.2 Evidence from two low-quality and three medium-quality observational studies of varying periods of follow-up, with a total of 1597 patients, showed that between 21% and 43% of patients who had an anaphylactic reaction experienced a recurrent reaction.

Cianferoni (2004) reported 14 recurrent reactions in a population of 46 (30%). Decker (2008) reported 45 cases in a population of 211 patients (27%), Mehl (2005) 28 cases in 103 patients (35%), Múgica Garcia (2010) 325 cases in 933 patients (34.8%), and Mullins (2003) 130 cases in 304 patients (43%).

3.3.3.3 Medium-quality evidence from one observational study, with a total of 304 patients of whom 130 had a recurrent reaction, indicated a median of two recurrent reactions per person, with a range of 0 to 18.

3.3.3.4 Evidence from two medium-quality studies suggested that women were at higher risk of recurrent reactions than men.

Decker (2008) reported a relative risk of recurrence in women of 2.14 (95% confidence interval [CI] 1.17 to 3.9). Mullins (2003) stated that women were at higher risk of recurrence than men; no figures were provided.

3.3.3.5 Evidence from one medium-quality (p = 0.535) and one low-quality observational study found that age was not associated with an increased risk of recurrence.

3.3.3.6 One medium quality observational study of 211 patients found that ethnicity was not associated with an increased risk of recurrence (p = 0.743).

3.3.3.7 *Evidence from two low-quality observational studies found that a range of allergens was proposed as the cause of the recurrent reaction. In addition, in 33% to 72% of cases the recurrent reaction was likely to be due to the same allergen that caused the first anaphylactic reaction.*

Mehl (2007) found food to be the cause in 71% of cases, insect sting in 7% of cases and specific immunotherapy in 7%, with an unknown trigger in 14% of cases. Múgica Garcia (2010) found that where the same allergen was the cause of the recurrent reaction that the following allergens were believed to be the cause: latex in 73% of cases, food in 39%, hymenoptera venom in 33% and an unknown trigger in 33%.

c) Who should be given an emergency treatment plan and when should that include an adrenaline injector?

3.3.3.8 No evidence was found on who should be given an adrenaline injector pending the referral appointment.

3.3.4 Health economic modelling

Referral to specialist allergy clinics (review question 3b) and the provision of adrenaline injectors (review question 3c) were identified as the highest economic priorities by the GDG. This was because of the high variation in practice and uncertain cost implications in these key areas. To address these issues, a health economic analysis was conducted by Kleijnen Systematic Reviews. Review question 3a was not considered to be a priority for health economic modelling.

The decision problems for the health economic analysis were:

- the cost effectiveness of referral to a specialist allergy service for definitive diagnosis of anaphylaxis and long-term management
- the cost effectiveness of adrenaline injectors for the treatment of anaphylaxis including the cost implications of training in their use.

No directly relevant cost-effectiveness papers were identified in the assessment group's literature search, so a new cost-effectiveness analysis was conducted. A Markov model was developed to incorporate short-term and long-term outcomes.

Methods

Both decision problems were addressed using a single model. This was deemed appropriate because the questions focused on similar outcome measures – that is, the costs and effects of the interventions in the prevention and/or management of recurrent anaphylactic reactions. As a result, the model simulated four comparators:

- referral to specialist allergy service with adrenaline injectors
- referral to specialist allergy service without adrenaline injectors
- standard care with adrenaline injectors, and
- standard care without adrenaline injectors.

The model comprised four states representing people at risk of recurrence, people experiencing a recurrence, people whose condition had remitted and death. A schematic diagram of the model structure is shown in figure 1.

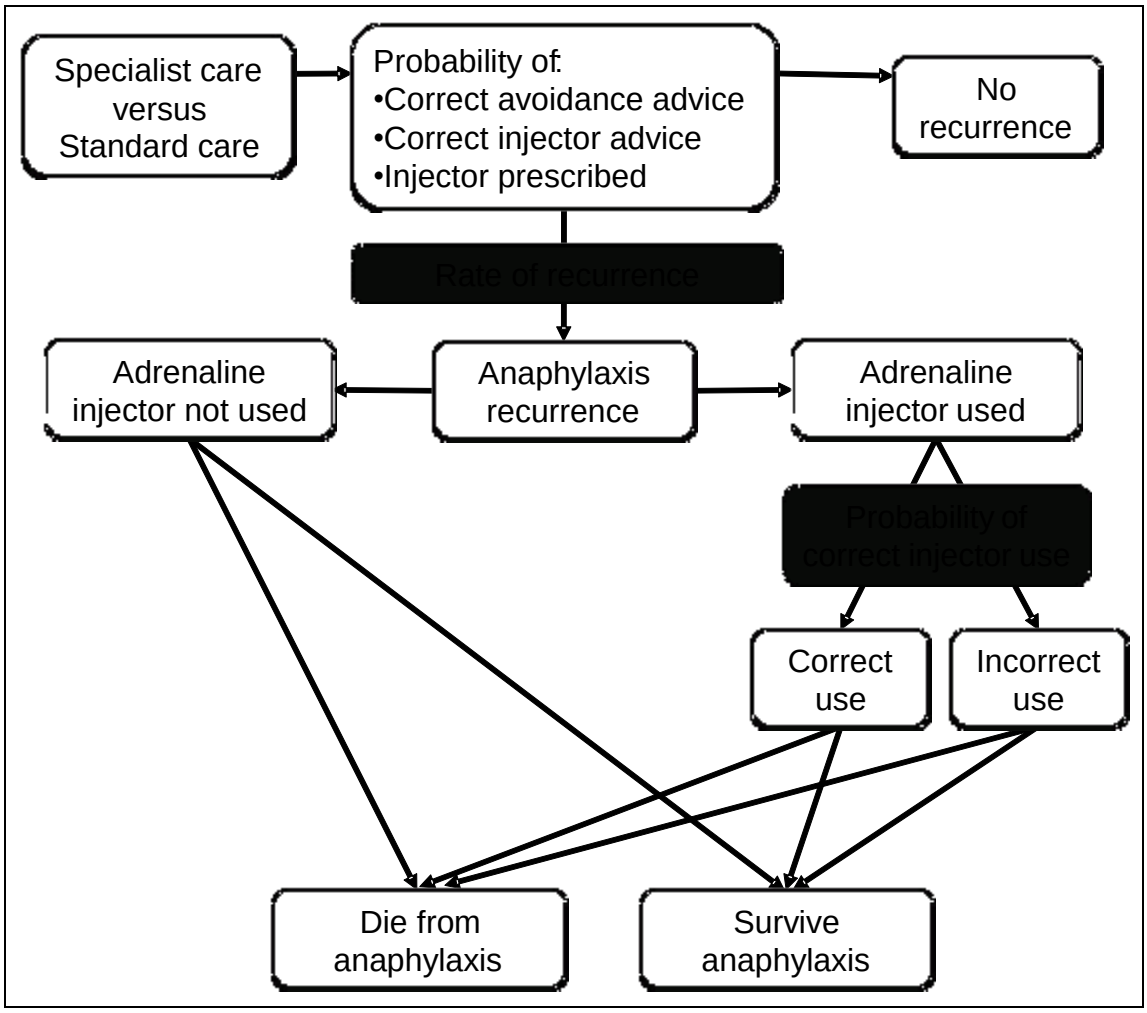


Figure 1 Schematic diagram of economic model

The population examined comprised people who had received emergency treatment for suspected anaphylaxis. In its base case, the model assumed an adult population (mean starting age of 30); an additional analysis simulated a paediatric setting (mean starting age of 5).

The modelled population was stratified according to four triggers of anaphylaxis: drugs, food, insect stings/venom and idiopathic. Standard care constitutes GP consultation only with no referral to allergy specialist services. The GDG agreed that this was a reflection of current practice.

The model was run over a lifetime horizon. Shorter time horizons were investigated in sensitivity analyses. A cycle length of 3 months was chosen as a period during which multiple recurrences were unlikely. The model's

sensitivity to parameter uncertainty was explored in deterministic (one-way and threshold) and probabilistic sensitivity analyses.

Model assumptions

Model methods are discussed in detail in appendix F. Key assumptions included the following.

- There are four mutually exclusive triggers of anaphylaxis: drug, food, insect/venom and idiopathic.
- Standard care comprises referral to a GP after anaphylaxis and no further investigation or treatment.
- Treatment in a specialist allergy service comprises:
  - GP costs as included in standard care
  - two initial appointments with a consultant-led specialist team, at which the diagnosis is confirmed, advice is given on avoidance of the trigger (if there is one) and, in the specialist allergy service with adrenaline injectors strategy, information is provided about the correct use of adrenaline injectors
  - for people with food-related anaphylaxis, follow-up appointments once every 2 years
  - for people with venom-related anaphylaxis, treatment with venom immunotherapy is possible (60% of people choose to undergo treatment; 20% of these drop out before completion)
  - for people with idiopathic anaphylaxis, 50% receive drug therapy for 2–3 months, but no additional follow-up appointments
  - for people with drug-related anaphylaxis, no additional follow-up.
- Recurrence rates are dependent on the trigger.
- When compared with people receiving standard care, people receiving specialist allergy service benefit from:
  - reduced incidence of recurrence, as a result of effective avoidance advice and/or immunotherapy
  - higher probability of successful adrenaline injector use, reflecting personalised instruction in how and when to use the injectors

  - higher quality of life (utility), as a result of reduced anxiety and symptoms in a well-managed condition.
- When compared with people without adrenaline injectors, people receiving adrenaline injectors benefit from:
  - reduced risk of mortality
  - higher quality of life (utility), as a result of reduced anxiety about the potential impact of a recurrence.
- Adrenaline injectors, if used successfully, would be used within 4.6–9.9 minutes of exposure to the trigger, and would prevent all deaths that would occur in the absence of adrenaline injectors. Deaths that occur within 4.5 minutes of exposure are not prevented, whether people are carrying adrenaline injectors or not.
- For people with idiopathic anaphylaxis, spontaneous remission is possible.
- Except where influenced by remission or treatment, the probability of recurrence remains constant throughout a person's life.
- The cost of recurrence relates to hospital admission only – that is, no additional follow-up costs are included.

Model parameters

The probability of trigger varied between adults and children. Values are summarised in table 10. Assumed recurrence rates, according to trigger type and treatment allocation, are summarised in table 11.

The effect of adrenaline injectors in reducing mortality was calculated based on data concerning time from trigger exposure to death, and estimates of emergency ambulance response times, drawn from published literature. The implication here is that timely and correct use of adrenaline injectors would prevent deaths that might occur before emergency services arrive. Key inputs are presented in table 12; see appendix F for full details.

The likelihood of mortality from causes other than anaphylaxis was modelled using age- and gender-specific mortality drawn from Office for National Statistics 2011 life-tables for England and Wales.

Health-related quality of life was estimated using general population utility data, adjusted by a decrement reflecting ongoing risk of recurrence. It was assumed that the reassurance and symptom control provided by a specialist allergy service would reduce this utility decrement, as would the provision of adrenaline injectors.

Full details of model parameters, their sources and the ranges across which they were varied in probabilistic sensitivity analysis are provided in appendix F.

Table 10 Probabilities of trigger assumed in economic model

Trigger	Proportion of population with specified trigger
Drugs	Adults 44.1%; children 12.4%
Food	Adults 12.5%; children 44.2%
Venom	13.4%
Idiopathic	30.0%

Table 11 Annual recurrence rates assumed in economic model

Trigger	Annual rate of recurrence per patient (range used in probabilistic model)	
	Under standard care	Under specialist service
Drugs	0.12 (0.05–0.19)	0.001 (0–0.002)
Food	0.11 (0.05–0.16)	0.01 (0–0.02)
Venom	0.1 (0.05–0.15)	0.1 (0.05–0.15)[a]
Idiopathic	0.28 (0.05–0.51)[b]	

[a] Under specialist service, the rate of recurrence decreases over time, in reflection of successful immunotherapy

[b] No difference between standard care and specialist service

Table 12 Additional key parameters in economic model

Parameter	Value
Probability of dying from an anaphylactic reaction given current provision of emergency services and adrenaline injector use	0.57%
Probability of dying from an anaphylactic reaction given current provision of emergency services and **no** adrenaline injector use	0.84%
Probability of dying from an anaphylactic reaction given current provision of emergency services and **successful** adrenaline injector use	0.03%
Probability of correct injector use with SC in children	66.7%
Probability of correct injector use with SC in adults	42.6%
Probability of correct injector use with SS (children and adults)	90.0%
Utility decrement associated with ongoing susceptibility to anaphylaxis	0.08
Days' quality of life lost per recurrence	5
Cost of adrenaline injectors	£26.45
Cost of inpatient treatment per recurrence	£469.88
Cost of SS appointments (consultant-led multidisciplinary team)	
- initial appointment (adults)	£321
- follow-up appointments (adults)	£450
- initial appointment (children)	£266
- follow-up appointments (children)	£234
Number of adrenaline injectors provided per year (assumes two devices to be available at any one time with a shelf-life of 12 months each)	4
Abbreviations: SC, standard care; SS, specialist service.	

Results

Base-case results – clinical outcomes

The model predicts that, over a lifetime, the number of recurrences experienced is strongly influenced by both trigger and treatment allocation (figure 2). Under standard care, people whose initial anaphylactic reaction was due to drugs, food or venom are expected to experience 5–6 further reactions in their lives. Under specialist allergy service, those figures are substantially reduced: the model predicts that less than 1-in-2 people with food-related anaphylaxis will experience a recurrence at any stage, and the incidence of drug-related recurrences is almost eradicated. For people with venom-related anaphylaxis, recurrence rates are approximately halved, to around 2.5 lifetime reactions per person; this reduction is due to the simulated effects of immunotherapy (the effect is less than that seen in food and drug-

related anaphylaxis because trigger avoidance is impractical in this aetiology). The incidence of idiopathic recurrences is similar across all strategies, and substantially lower than that seen for other triggers; this is because the model assumes an ongoing rate of spontaneous remission in this group of people, so the number at risk of recurrence diminishes as time goes on. The differences between strategies with adrenaline injectors and those without are minimal; it should be clear that injector use does not, in itself, prevent recurrences, though it may mitigate their consequences.

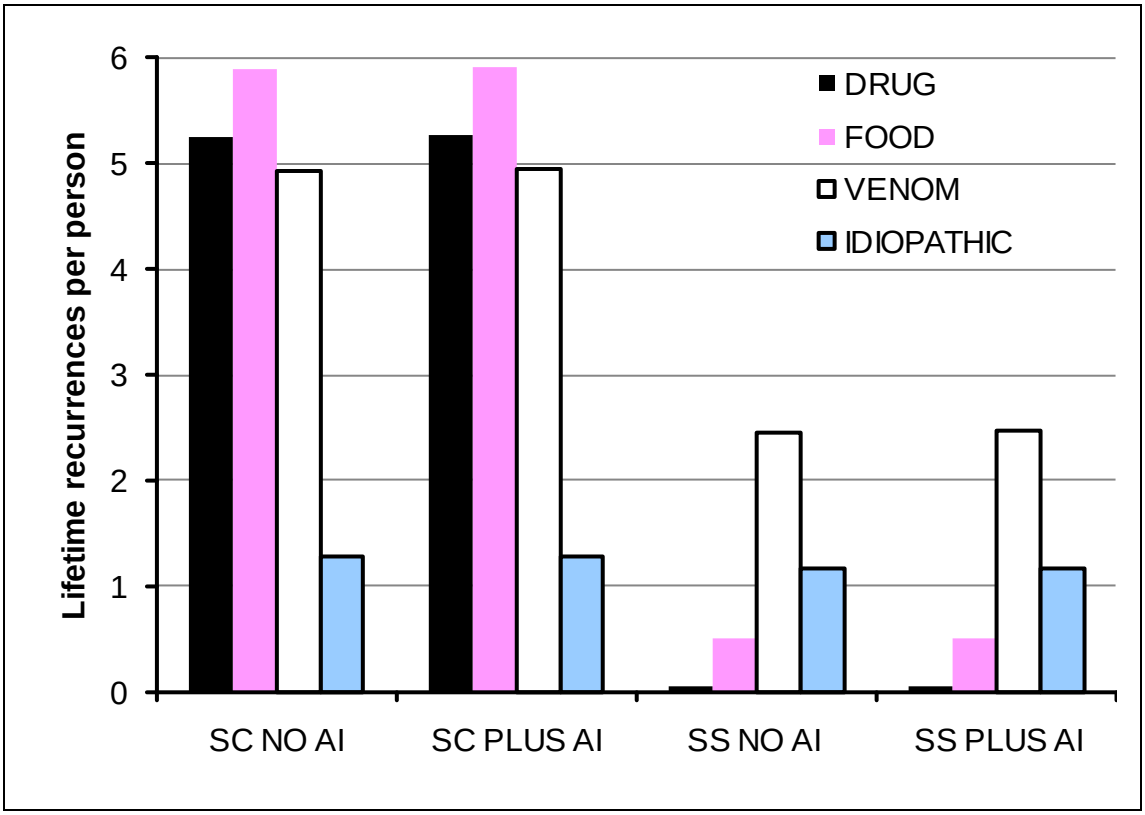


Figure 2 Recurrence rates predicted in the economic model

A similar pattern was seen with the predicted rate of anaphylaxis-related deaths (figure 3). The model predicts that, with standard care without adrenaline injectors, 6–8% of people with food, drug or venom-related anaphylaxis will die as a consequence of a recurrence. For people with food- and drug-related anaphylaxis, those figures drop to less than 1% with specialist allergy service; however, for the reasons discussed above, people with venom-related anaphylaxis experience a less marked reduction in mortality. The effect of adrenaline injectors can also be seen in figure 3: the

risk of death from recurrence is 10% to 30% lower in people with injectors than in those without.

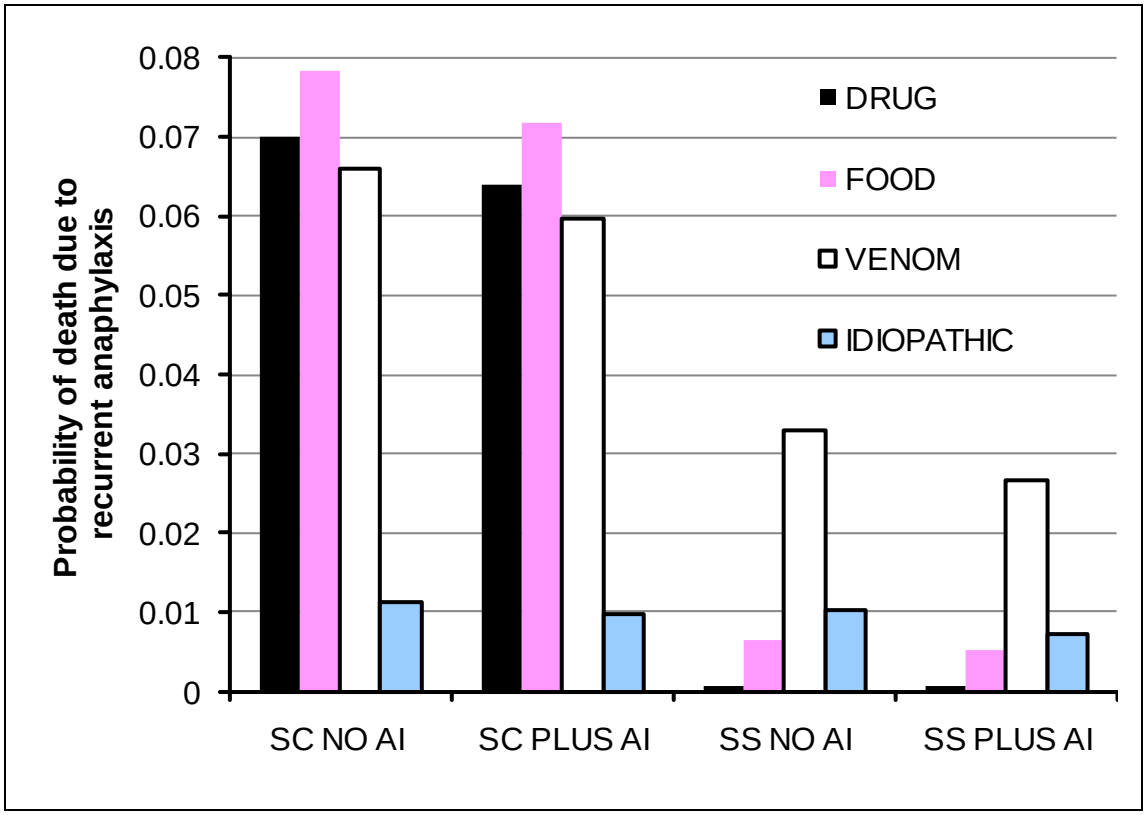


Figure 3 Mortality rates predicted in the economic model

Table 13 shows the model's predicted mortality rates in terms of number needed to treat to prevent one death from recurrent anaphylaxis. It can be seen that, other than in people with idiopathic anaphylaxis, for whom the efficacy of the modelled interventions appears relatively slight, the effect of specialist allergy service appears to be substantial. When compared with standard care, specialist allergy service strategies are predicted to result in one fewer death per 22–25 people treated across the whole population. The effect of adrenaline injectors is less marked: under specialist allergy service, a little over 500 people would have to receive injectors to prevent one death from recurrence whereas, under standard care, the equivalent figure is approximately 200. The effect is especially small with drug-related anaphylaxis under specialist allergy service. This is because specialist allergy service is assumed to remove the risk of drug-related anaphylaxis almost entirely; therefore, the opportunity for injectors to have a life-saving effect is very slight.

Table 13 Economic model prediction – number needed to treat to prevent one death from recurrent anaphylaxis

Trigger	SS plus AI versus			SS no AI versus		SC plus AI versus
	SS no AI	SC plus AI	SC no AI	SC plus AI	SC no AI	SC no AI
Drug	7879	16	14	16	14	166
Food	877	15	14	15	14	155
Venom	155	30	25	37	30	161
Idiopathic	343	409	253	−2104[a]	960	659
Average[b]	**516**	**24**	**22**	**25**	**23**	**210**

[a] Negative number needed to treat implies number needed to harm – the number of people who would need to be treated with specialist allergy service without adrenaline injectors before one additional death would be expected compared with mortality under standard care with adrenaline injectors

[b] Weighted according to relative prevalence of trigger types in model

Abbreviations: AI, adrenaline injector; SC, standard care; SS, specialist service.

Base-case results: cost–utility

In its base case, the economic model suggests that strategies including specialist allergy service are likely to be preferred to those based on standard care alone, and those strategies with adrenaline injectors are likely to be preferred to those without.

When compared with standard care without adrenaline injectors, specialist allergy service without adrenaline injectors is associated with health gains of around one quality-adjusted life year (QALY) per person at an average cost of approximately £760, resulting in an incremental cost-effectiveness ratio (ICER) of around £750 per QALY gained. Assuming conventional thresholds per QALY, this would reflect excellent value for money. Standard care with adrenaline injectors is dominated by (that is, more expensive and less effective than) specialist allergy service without adrenaline injectors, so would not be considered a viable option in an incremental analysis. Specialist allergy service with adrenaline injectors is predicted to accrue health gains of around 0.5 QALYs per person when compared with specialist allergy service without adrenaline injectors at an additional lifetime cost of around £925, resulting in an ICER of approximately £1800 per QALY gained. Once more, this would be considered to be a low ICER in the context of conventional thresholds. Therefore, if the modelled strategies are considered mutually exclusive

treatment options, specialist allergy service with adrenaline injectors is likely to be chosen as the most cost-effective approach.

The comparison between standard care without adrenaline injectors and standard care with adrenaline injectors may also be relevant when considering whether adrenaline injectors should be prescribed to people following emergency treatment for suspected anaphylaxis but before they have been seen by a specialist team (review question 3c). The model suggests that, as in the specialist allergy service setting, providing adrenaline injectors results in QALY gains of around 0.5 per person at an additional lifetime cost of around £900, resulting in an ICER of approximately £1650 per QALY gained. Again, this is likely to be considered good value for money.

Deterministic and probabilistic base-case results are presented in table 14. The deterministic and probabilistic results are very similar, indicating that the expected costs and QALYs are close to a linear function of the parameter values.

Table 14 Deterministic and probabilistic base-case results (adults at age 30)

Strategy	Cost (£)	Effect (QALYs)	Incremental		
			Cost (£)	Effect (QALYs)	ICER (£ per QALY)
Deterministic					
SC no AI	978.26	39.25			
SS no AI	1745.19	40.25	766.93	1.00	763.45
SC plus AI	1875.83	39.79	130.64	-0.46	(Dominated)
SS plus AI	2668.59	40.76	923.40	0.51	1808.13
Probabilistic (mean)					
SC no AI	981.13	39.22			
SS no AI	1744.40	40.25	763.27	1.03	742.01
SC plus AI	1879.96	39.76	135.56	-0.48	(Dominated)
SS plus AI	2668.52	40.76	924.12	0.51	1819.82

Abbreviations: AI, adrenaline injector; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard care; SS, specialist service.

The cost-effectiveness acceptability curve (figure 4) shows that specialist allergy service with adrenaline injectors has the greatest probability of being the most cost-effective option, unless the threshold is assumed to be lower than approximately £2000 per QALY gained, in which case specialist allergy service without adrenaline injectors would be the optimal choice.

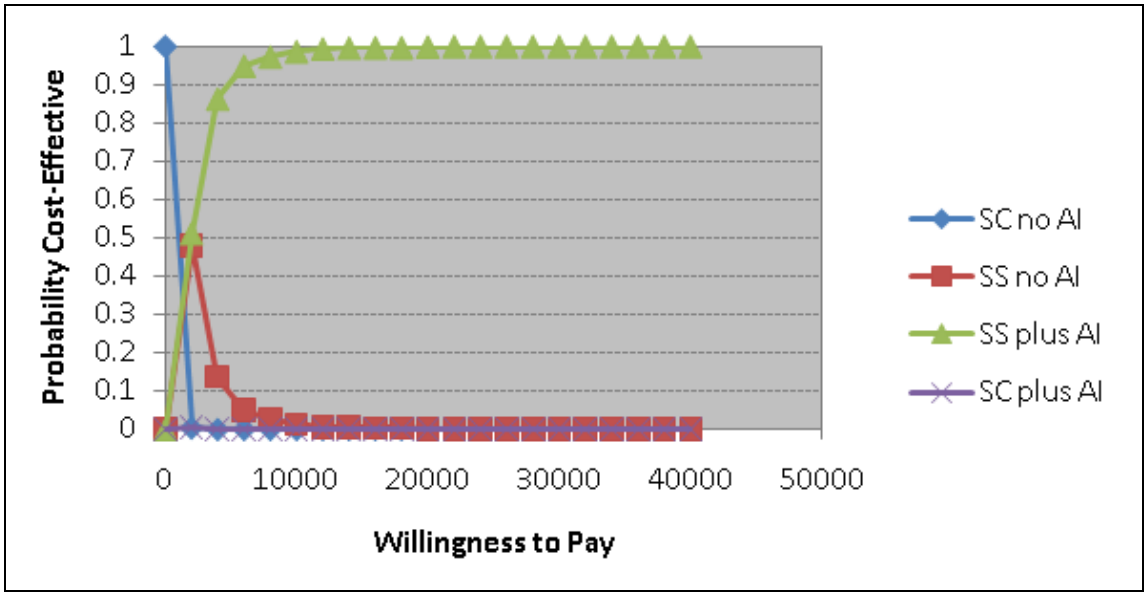


Figure 4 Cost-effectiveness acceptability curve

Results in children

A similar pattern of results was seen when the analysis was repeated for children with a mean age of 5. When compared with standard care, strategies including specialist allergy service generate health gains of nearly 2 QALYs per person at relatively small cost, so they would be likely to be preferred. Similarly, in strategies with adrenaline injectors, small additional costs are offset by QALY gains of around 0.8–0.9 per person, resulting in low ICERs. Results are tabulated in table 15.

Table 15 Deterministic results for children at age 5

Strategy	Cost (£)	Effect (QALYs)	Incremental		
			Cost (£)	Effect (QALYs)	ICER (£ per QALY)
SC no AI	1137.78	61.05			
SC plus AI	2551.18	61.96	1413.40	0.91	1548.69
SS no AI	3049.38	62.96	498.20	1.00	498.66
SS plus AI	4501.53	63.74	1452.15	0.78	1850.46

Abbreviations: AI, adrenaline injector; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard care; SS, specialist service.

Scenario analysis

Because no evidence was available to underpin the assumption that specialist services and adrenaline injectors attenuate the health-related quality of life (HRQoL) decrement associated with susceptibility to anaphylaxis, a scenario analysis was performed in which these benefits were removed. Cost–utility results are shown in table 16.

Table 16 Scenario analysis – deterministic results assuming specialist services and adrenaline injectors confer no ongoing utility benefit

Strategy	Cost (£)	Effect (QALYs)	Incremental		
			Cost (£)	Effect (QALYs)	ICER (£ per QALY)
Adults (mean age 30)					
SC no AI	978.26	39.25			
SS no AI	1745.19	39.79	766.93	0.55	1398.99
SC plus AI	1875.83	39.35	130.64	-0.44	(Dominated)
SS plus AI	2668.59	39.85	923.40	0.05	17,175.35
Children (mean age 5)					
SC no AI	1137.78	61.05			
SC plus AI	2551.18	61.32	1413.40	0.28	5123.38
SS no AI	3049.38	62.29	498.20	0.97	514.44
SS plus AI	4501.53	62.41	1452.15	0.12	12,610.76

Abbreviations: AI, adrenaline injector; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SC, standard care; SS, specialist service.

In these analyses, the value of specialist services, when compared with standard-care strategies, remains clear. Although QALY gains are

approximately halved, compared with the base-case analysis, ICERs remain relatively low, suggesting good value for money. Results for adrenaline injectors are affected to a greater degree; this shows that the QALY gains predicted in the base case are predominantly ascribable to the assumed reduction in anxiety and consequent improvement in day-to-day HRQoL. However, a small QALY benefit remains, reflecting the effect of adrenaline injectors in reducing mortality, and this would normally be considered sufficient to outweigh the costs entailed in their use (assuming a threshold of £20,000 per QALY or more).

The base-case model effectively assumes that all simulated individuals have been correctly diagnosed as experiencing anaphylaxis and, hence, are at risk of future recurrence. This may be unrealistic, so a second scenario analysis was performed in which a proportion of people were assumed to have received a false-positive diagnosis of anaphylaxis. For these people, the costs of specialist services and/or adrenaline injectors were incurred, but the probability of recurrence was set to zero, thereby removing the potential for benefit in reduced risk of mortality. The results of this scenario differed only slightly from those generated in the base case, as the day-to-day benefit of specialist services and/or adrenaline injectors was assumed to persist in people who were not, in fact, at risk of recurrence. When this benefit was removed, as in the scenario above, the impact of false-positive diagnoses was greater; however ICERs remained less than £20,000 per QALY where the rate of misdiagnosis was 20% or less.

Sensitivity analysis – threshold analyses

Threshold analysis was conducted on all parameters, with the assumed value of each varied over a broad range to identify the level at which cost-effectiveness conclusions would be altered, assuming a conventional threshold of £20,000 per QALY. These analyses suggested that specialist allergy service with adrenaline injectors remains the most cost-effective option, with few exceptions:

- standard care with adrenaline injectors would become the most cost-effective option if:

  - the rate of recurrence in drug-related anaphylaxis for people under standard care exceeded 0.09 per year (base case: 0.001)
  - the rate of recurrence in food-related anaphylaxis for people under standard care exceeded 0.35 per year (base case: 0.01)
- specialist allergy service without adrenaline injectors would become the most cost-effective option if:
  - the probability of dying with a successfully used injector exceeds 0.03 (base case 0.000252)
  - the cost per injector exceeds £146 each (base case: £26.45)
  - injectors are associated with a utility gain of less than 3% when compared with strategies without injectors (base case: 25%)

Therefore, the model was considered robust to univariate sensitivity analysis except at relatively extreme values of a few parameters. Analysis of the model's time horizon indicated that specialist allergy service with adrenaline injectors becomes less likely to be cost effective as the time horizon becomes shorter. However, the key ICERs remain under £20,000 per QALY for analyses in which the time horizon is 3 years or more (for adults) or 2 years or more (for children).

Interpretation and limitations

The model suggests that the interventions examined – referral to specialist allergy service and the use of adrenaline injectors – provide health gains at relatively low costs. Therefore, strategies that incorporate these interventions appear to be an effective use of NHS resources.

Referral to a specialist allergy service was predicted to be associated with substantially increased life expectation and improved quality of life at negligible additional cost. Similarly, evidence from the comparison of standard care without adrenaline injectors with standard care with adrenaline injectors suggests that good value for money can be expected from providing adrenaline injectors to people who have had a suspected anaphylactic reaction (as an interim measure before they are seen by a specialist service). This was the case even though the model assumed that the probability of correct injector use was relatively low in such people when compared with the

probability of successful use when they go on to receive training from a specialist service. Moreover, sensitivity analyses in which the time horizon was shortened demonstrated that the ICER remained very low even when the period of interest was restricted to the minimum that could be simulated in the model. This suggests that short-term gains for adrenaline injectors are predicted to be sufficient to justify their cost in the period pending a specialist appointment.

It should be acknowledged that several critical parameters were based on GDG opinion in the absence of relevant published data. In particular, the effectiveness of the interventions in reducing recurrence and increasing quality of life was largely reliant on expert opinion. Nevertheless, model results appeared robust to parameter uncertainty: variations in inputs produced different results only when relatively implausible values were adopted. To examine the model's sensitivity to these important assumptions further, an additional sensitivity analysis was performed, in which all recurrence rates for people under the care of specialist services were varied simultaneously. This analysis suggested that the recurrence rates assumed for strategies including specialist services would have to be at least 6–8 times greater before standard care would be judged to provide better value for money. A related two-way sensitivity analysis varying recurrence rates with and without specialist services was also performed. It showed that standard care would be preferred only if recurrence rates with specialist services were four times too low in the base-case model and recurrence rates under standard care were four times too high. In combination, these analyses suggest that model results are valid unless the base-case recurrence rates are very poor estimates of the true values.

Similarly, GDG opinion was used to determine the likely effect of specialist services and adrenaline injectors in attenuating the HRQoL decrement associated with susceptibility to anaphylaxis. When this assumed benefit was entirely removed, the cost effectiveness of both specialist services and adrenaline injectors was reduced; however, ICERs for each option remained within the range normally considered to represent effective use of NHS

resources. This conservative analysis provides reassurance that model results are not solely dependent on the assumed day-to-day HRQoL benefit.

An additional multiway sensitivity analysis showed that, when no ongoing HRQoL benefit is assumed, recurrence rates under specialist services would have to be at least four times higher than their base-case values for standard care to become the preferred option (assuming a threshold of £20,000 per QALY).

Another limitation of this analysis is that it effectively assumes that the resources to provide specialist allergy services are immediately available. In reality, there are likely to be additional set-up costs associated with establishing the necessary additional capacity, which the economic model does not capture. GDG opinion suggested that such costs would relate predominantly to the training of clinicians, as little specialist equipment is necessary to provide the service. To explore this issue, a sensitivity analysis was performed in which an additional cost was associated with each modelled individual's first specialist appointment. This analysis suggested that strategies including specialist services remain associated with ICERs lower than £20,000 per QALY unless this additional cost exceeds £15,000. Therefore, set-up costs would only make a qualitative difference to findings if they can be assumed to exceed an equivalent of £15,000 for each patient who would benefit from the service over the lifetime of the resource.

It may be argued that, by treating standard care and specialist services as mutually exclusive, the model provides an unrealistic representation of current clinical reality, in which a small number of specialist services already see a proportion of people who have experienced suspected anaphylaxis. Given that such people find their way to specialist services, it theoretically may not be necessary to recommend routine referral. However, the economic model does not support this view. For example, if might be assumed that, in current practice, people will be referred to specialists following their first recurrence (second reaction) of anaphylaxis. The recurrence rates assumed in the model suggest that, under standard care, people experience approximately one recurrence per 10 years, so it can be estimated that people are referred to

specialists, on average, around 10 years after their initial anaphylaxis. The fact that the model suggests specialist services provide an effective use of NHS resources when the time horizon is constrained to 2–3 years may therefore be seen as evidence that additional benefit is gained following a strategy of routine referral long before the average person would have reached specialist services by an informal route.

There is uncertainty over the true shelf-life of adrenaline injectors in practice, because it is based on time from manufacture, rather than time from prescription. As a result, the expiry date of any dispensed device depends on factors that vary between individual suppliers and pharmacies. For this reason, the model conservatively assumed that each device would have a lifetime of 12 months, even though they are manufactured with shelf-lives of up to 24 months. If this assumption leads to an overestimate of the frequency with which injectors need replacing, the ICERs for strategies including adrenaline injectors may be somewhat too high. However, sensitivity analyses demonstrated that assumptions around resource use associated with injectors do not have a major influence on model outputs, so results are not materially affected by any inaccuracy.

The model's assumption that specialist services do not limit the incidence of recurrence in idiopathic anaphylaxis may also produce conservative ICERs. The costs of drug therapy in a proportion of cases are incorporated in the model, but the effects are uncertain. It is possible, therefore, that the benefits due to specialist service in people with idiopathic anaphylaxis are underestimated.

These results must also be considered in the context of substantial structural uncertainty. Without direct evidence as to the costs and effects of the interventions being simulated, it was necessary for the model to rely on a range of assumptions that are difficult to verify. For example, many assumptions and several sources of data were required in order to estimate the effect that adrenaline injectors have in attenuating mortality risk due to recurrent anaphylaxis. It is possible that, were empirical data to become

available in this and other areas, a different model structure would become possible and a different cost–utility picture might emerge.

It should also be emphasised that the costs and effects of healthcare programmes that seek to minimise the incidence of recurrent anaphylaxis are difficult to distinguish from the costs and effects of the management of chronic allergy (which is beyond the scope of this guideline). For example, it is possible that the economic analysis underestimates the benefits attributable to routine follow-up in specialist services by limiting its focus to a single outcome (anaphylactic reactions).

3.3.5 Evidence to recommendations

Review question: What should be part of the review after a reaction to confirm the diagnosis and guide referral?

Relative value of different outcomes	The GDG discussed current clinical practice when performing a review, such as patient history of comorbidities and previous allergen exposures. It was agreed that the aim of the clinical review after a suspected anaphylactic reaction is to rule out other potential diagnoses and to help identify the possible trigger before the person is seen by a specialist allergy service. It is important for the clinician to record the key signs and symptoms of the suspected anaphylactic reaction so that the post-emergency care treatment provided is appropriate. The GDG also agreed that the review should collect data on the timing of the onset of symptoms so that timed blood samples for mast cell tryptase testing can be taken appropriately.
Trade-off between clinical benefits and harms	The GDG considered that although there is an increased risk of anxiety from an incorrect diagnosis, this is acceptable because the clinical benefits would significantly outweigh the small risk of anxiety.
Economic considerations	Not applicable.
Quality of evidence	No evidence was identified.
Other considerations	It was acknowledged by the GDG that due to the lack of evidence, the recommendations were based on their expertise, knowledge and experience alone. The GDG noted that in order for these recommendations to be implemented appropriately, a clinical understanding of anaphylaxis and associated comorbidities is required by the clinician conducting the review.

Review question: Who should be referred, when and to where or whom?

Relative value of different outcomes	The GDG discussed the evidence, which showed a high rate of recurrence of anaphylactic reactions. The GDG therefore felt that referral to a specialist allergy service was warranted to help prevent further anaphylactic reactions. The GDG considered the mixed evidence that suggested women are at a higher risk of recurrent anaphylactic reactions than men. However, it was felt that a large proportion of men still suffer from recurrent reactions and that decisions on whether or not to refer should not be based on gender alone. The GDG noted that the evidence did not provide a clear picture as to whether susceptibility to specific allergens put people more at risk of a recurrent reaction. It was agreed that the final diagnosis of the causative agent should be carried out by a specialist. Therefore the GDG agreed that there is a need to refer all patients to a specialist allergy service, to help prevent the recurrence of anaphylaxis and reduce anxiety following emergency treatment. To ensure that the referral is made, the GDG agreed that the person should be referred prior to discharge. It was acknowledged that effective communication of the necessary information between the different parts of the NHS is important in ensuring optimum care. However, the GDG was of the opinion that in the main this is standard practice within the NHS.
Trade-off between clinical benefits and harms	The GDG considered that although there is an increased risk of anxiety from unnecessary referral, this is acceptable because the clinical benefits would significantly outweigh the small risk of anxiety.
Economic considerations	The health economic analysis indicates that identifying specific allergy trigger(s) and the resultant reduction in rates of recurrence of anaphylaxis, along with the ongoing HRQoL benefit associated with reduced anxiety, is of value to the NHS. The analysis was robust to extreme variation in cost and effects. Therefore, referring all people who have had treatment for suspected anaphylaxis to specialist allergy services would be cost effective.
Quality of evidence	Low to medium quality evidence with conflicting results was identified. The recommendations were based on GDG consensus.
Other considerations	The GDG could not identify subgroups of people who should not be referred because of the risk of missing people who are potentially at high risk of recurrence.

Review question: Who should be given an emergency treatment plan and when should that include an adrenaline injector?

Relative value of different outcomes	The GDG agreed the importance of quickly treating any subsequent reactions while the person is waiting to be seen by the allergy service. The GDG stated that the aim of offering an

	adrenaline injector is to prevent adverse outcomes from subsequent anaphylactic reactions.
Trade-off between clinical benefits and harms	The GDG considered that there is a risk of harm associated with the improper use of the adrenaline injector, such as the failure to administer adrenaline appropriately. The GDG took into account the high rate of recurrence of anaphylaxis and the time constraints of referral to specialist allergy services. The GDG concluded that the risk of harm was offset by the considerable benefits of preventing adverse outcomes from a recurrent anaphylactic reaction. In addition it was felt that the risk of a person using an adrenaline injector inappropriately could be reduced if adequate training on when to use the injector and a demonstration on how to use it were provided prior to discharge. It was felt that this would be sufficient as an interim measure before the specialist allergy appointment. It was acknowledged that some people, for example those with cardiac problems, could have adverse events as a result of using an adrenaline injector. However, the GDG felt that the prescription of an adrenaline injector in these cases should be at the discretion of the clinician in question. The GDG acknowledged that there are issues relating to the appropriate prescription of adrenaline injectors for children, specifically around the doses required. Although it was not within the remit of the guideline to comment upon the required dose, the GDG felt it necessary to highlight within the recommendations that an appropriate adrenaline injector should be prescribed.
Economic considerations	The health economic analysis indicates that the routine provision of adrenaline injectors is of value to the NHS, primarily because it is expected to reduce the risk of death from recurrent anaphylaxis. The value of this reduction is sufficient to justify the cost implications of providing the devices and training people to use them. Thus, providing adrenaline injectors as an interim measure for people who have had treatment for suspected anaphylaxis is considered to be a cost-effective practice.
Quality of evidence	No evidence was identified.
Other considerations	It was acknowledged by the GDG that due to the lack of evidence, the recommendations were based on their expertise, knowledge and experience alone. The GDG was unable to state the exact number of adrenaline injectors to be prescribed per person because this would depend on various individual factors. Instead any decision should be taken by the clinician in question.

3.3.6 Recommendations and research recommendations for assessment after a suspected anaphylactic reaction

Recommendations

Recommendation 1.1.1

Document the acute clinical features of the suspected anaphylactic reaction (rapidly developing, life-threatening problems involving the airway [pharyngeal or laryngeal oedema] and/or breathing [bronchospasm with tachypnoea] and/or circulation [hypotension and/or tachycardia] and, in most cases, associated skin and mucosal changes).

Recommendation 1.1.2

Record the time of onset of the reaction.

Recommendation 1.1.3

Record the circumstances immediately before the onset of symptoms to help to identify the possible trigger.

Recommendation 1.1.9

After emergency treatment for suspected anaphylaxis, offer people a referral to a specialist allergy service (age-appropriate where possible) consisting of healthcare professionals with the skills and competencies necessary to accurately investigate, diagnose, monitor and provide ongoing management of, and patient education about, suspected anaphylaxis.

Recommendation 1.1.10

After emergency treatment for suspected anaphylaxis, offer people (or, as appropriate, their parent and/or carer) an appropriate adrenaline injector as an interim measure before the specialist allergy service appointment.

Research recommendations

See appendix B for full details of the research recommendations.

Research recommendation B4

What is the annual incidence of anaphylaxis and its related outcomes within the UK?

3.4 Patient information after a suspected anaphylactic reaction

3.4.1 Review question

What information do people need after an anaphylactic reaction, and before referral?

3.4.2 Evidence review

A total of 2659 articles were found by systematic searches. After the screening of titles and abstracts, 2648 references were excluded. A total of 11 papers were obtained and the full texts screened. A total of 4 studies were included (for a full list of included and excluded studies, see appendix D).

Studies were considered relevant if they included any types of patient information for adults, children, young people and their parents/carers following a suspected anaphylactic reaction and before referral to a specialist allergy service. The studies were reviewed and the quality established. The main themes from the evidence were extracted and presented to the GDG in the form of a summary table (see table 16).

Table 16 Summary of included studies

			Key themes			
Study	**Study type**	**Study quality**	**Avoidance advice**	**General anaphylaxis education**	**Use of adrenaline injectors**	**Details of follow-up**
Kastner (2010)	Systematic review investigating gaps in anaphylaxis management	Moderate	Patients lacked knowledge of trigger avoidance.	Patients identified gaps in following an anaphylaxis management plan.	Patients lacked knowledge of using adrenaline injectors.	Follow-up was not identified as a key theme.
Simons (2011)	Summary of World Allergy Organisation guidelines	Moderate	Clinicians should provide personalised written instructions about avoiding the confirmed trigger, including various alternative names, for example casein for milk.	Advise patients they are at increased risk of future anaphylactic reactions. Advise patients that they have experienced a potentially life-threatening medical emergency. Provide an anaphylaxis emergency action plan that helps them to recognise anaphylaxis symptoms.	Patients should be taught why, when and how to inject adrenaline.	Advise patients that they require a follow-up by an allergy/immunology specialist.
Danica (2008)	Opinion piece	Very low	Provide information on prevention strategies.	Healthcare professionals should educate patients on symptoms of anaphylaxis.	Patients should be taught how to use adrenaline injectors.	Follow-up was not identified as a key theme.
Lieberman (2007)	Opinion piece	Very low	Provide advice on avoiding trigger.	Advise patients there is a risk of recurrence.	Patients should be provided with instructions on the use of adrenaline injectors and when to use them.	Advise the patient that they require a follow-up with an allergy specialist.

See appendix E for the evidence tables in full.

3.4.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

3.4.3.1 *Evidence from two moderate-quality and two very low-quality studies suggested that before discharge patients with suspected anaphylaxis should be provided with advice on avoiding the suspected trigger(s) and on how and when to use an adrenaline injector.*

3.4.3.2 *Evidence from two moderate-quality and two very low-quality studies suggested that before discharge patients with suspected anaphylaxis should be given general education on anaphylaxis (signs, symptoms and severity).*

3.4.3.3 *Evidence from two moderate-quality and two very low-quality studies suggested that patients with suspected anaphylaxis should be given a written anaphylaxis emergency action plan or personalised written instructions on avoidance before discharge.*

3.4.3.4 *Evidence from one moderate-quality and one very low-quality study suggested that patients with suspected anaphylaxis should be provided with information about follow-up with an allergy service before discharge.*

3.4.4 Health economic modelling

A health economic analysis was not conducted for this question.

3.4.5 Evidence to recommendations

Relative value of different outcomes	The GDG considered the evidence on patient information for people who have emergency treatment for suspected anaphylaxis. The GDG discussed the importance of training patients in the correct use of an adrenaline injector because incorrect use can lead to worsening of anaphylactic symptoms. The GDG also discussed their experience of patients sustaining needle stick injuries as further support for proper training. The group agreed the importance of advising patients about when to use the adrenaline injector, including how to recognise the signs and symptoms of a biphasic reaction or a further anaphylactic reaction, and to call emergency services as soon as the adrenaline has been administered. The GDG discussed the importance of educating patients about anaphylaxis, including providing information about patient support groups and the importance of being referred to a specialist allergy service. The GDG considered that if the patient was aware of the importance of a correct follow-up it could reduce anxiety and lead to a correct diagnosis. The GDG agreed that patients should be advised to avoid the suspected trigger (if known); however they considered that detailed information relating to management plans or avoidance strategies should be provided in a specialist setting where allergy specialists are trained in providing management plans.
Trade-off between clinical benefits and harms	Not applicable.
Economic considerations	Not applicable.
Quality of evidence	Evidence was used from a variety of sources: two moderate-quality studies (World Allergy Organisation summary and a systematic review of patient knowledge) and two very low-quality studies (opinion pieces).
Other considerations	The GDG noted that clinical expertise of anaphylactic reactions is required when implementing these recommendations, especially when training people in the use of adrenaline injectors.

3.4.6 Recommendations and research recommendations for patient information

Recommendations

Recommendation 1.1.11

Before discharge a healthcare professional with the appropriate skills and competencies should offer people (or, as appropriate, their parent and/or carer) the following:

- information about anaphylaxis, including the signs and symptoms of an anaphylactic reaction
- information about the risk of a biphasic reaction
- information on what to do if an anaphylactic reaction occurs (use the adrenaline injector and call emergency services)
- a demonstration of the correct use of the adrenaline injector and when to use it
- advice about how to avoid the suspected trigger (if known)
- information about the need for referral to a specialist allergy service and the referral process
- information about patient support groups.

Research recommendations

No research recommendations have been made for this question. See appendix B for full details of the research recommendations.

3.5 Models of care for the diagnosis of anaphylaxis

3.5.1 Review question

What model or organisation of care should be adopted to improve the diagnosis of anaphylaxis post-reaction?

3.5.2 Evidence review

A total of 3494 articles were found by systematic searches. Full text was ordered for 14 articles based on the title and abstract. References cited in the

2006 review commissioned by the Department of Health on interventions and services available for the treatment and diagnosis of allergies (Lockwood et al. 2006) and in the 2010 update of the Joint Task Force on Practice Parameters diagnosis and management of anaphylaxis guidelines (Lieberman et al. 2010) were also checked; a further two articles were ordered.

No studies met the eligibility criteria evaluating different models of care in the diagnosis of anaphylaxis (for the full review protocol and inclusion and exclusion criteria, see appendix C). Because of the lack of any relevant studies, five studies were considered as 'indirect' evidence, and were presented to the GDG. These included one systematic review (Kastner et al. 2010), one retrospective record review (Krøigaard et al. 2005), two referral guidelines (Sweetman et al. 2006, Waserman et al. 2010) and one narrative review (Zeiger and Schatz 2000).

The GDG used the 'indirect' studies to prompt discussion of current practice and variation. The recommendations were therefore based on the expertise of the GDG and their knowledge of current national guidance for allergy services.

Table 17 Summary of studies ('indirect' evidence)

Author (year)	Study design	Outcomes
Kastner (2010)	Systematic review	No specific recommendations on referral, but a general call for the development of interventional strategies and practice tools to address the knowledge and practice gaps in order to improve care.
Krøigaard (2005)	Retrospective record review	36/48 (75%) grade III and III+ reactions had a 'suggested' potential allergen; 25% had no suggested allergen. Overall, for all grades of reaction, of the 49/67 (73%) where a suggested cause was made, 31/67 (46%) had no allergen confirmed and 18/67 (27%) had other allergens found. 5/67 (7%) had a complete match between the suggested allergen and the investigation result. 13/67 (19%) had a partial match (because of additional allergens either suggested and not confirmed or confirmed but not suggested).
Sweetman (2006)	Referral guidelines	The following patients should be referred to an allergist–immunologist: Individuals with a severe allergic reaction (anaphylaxis) without an obvious or previously defined trigger. (After a severe allergic reaction without a known cause, a trigger should be identified if at all possible. An allergist–immunologist is the most appropriate medical professional to perform this evaluation, which might include skin testing, in vitro tests, and challenges when indicated [including with exercise, see below]. Major triggers for anaphylaxis are foods and food constituents, medications and biological agents, latex, and insect stings. Future avoidance of the identified triggers should prevent subsequent anaphylactic reactions. Management of idiopathic anaphylaxis by an allergist–immunologist is associated with a reduction in hospitalisations and emergency department visits.) People with anaphylaxis attributed to food. (Food allergy is the most common cause of anaphylaxis outside the hospital setting. Allergist–immunologists use diagnostic modalities to confirm the trigger and use their specific training and clinical experience to educate patients regarding avoidance and immediate management to prevent potentially deadly outcomes.) People with exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis. (After an anaphylactic reaction that appears to have a significant relationship to exercise, it is crucial to be certain whether exercise is the cause and to determine

		whether a food might be involved.) People with drug-induced anaphylaxis. (Allergist–immunologists use diagnostic agents to confirm the drug responsible for the reaction, if these agents are available.) Based on non-randomised controlled intervention studies, observational, cohort or case–controlled studies, and review articles or expert opinion.
Waserman et al. (2010)	Referral guidelines	Referral to an allergist: After acute anaphylaxis patients should be assessed for future risk of anaphylaxis. Include anybody who has any rapid onset systemic allergic reaction (gastrointestinal, respiratory, cardiac) or diffuse hives to any food or stings. Include anybody who has any rapid onset (minutes to hours) reaction of any severity to higher risk food such as peanuts, tree nuts, shellfish, sesame. If uncertain, refer patient to allergist for evaluation. Based on expert committee reports or opinions or clinical experience of respected authorities or both; or extrapolated from higher categories of evidence.
Zeiger and Schatz (2000)	Narrative review	Defined the allergist as 'the specialist called on to identify the cause of an anaphylactic reaction, to determine potential preventive measures, and to evaluate the patient who may need to receive a substance to which he or she has reacted previously.'

See appendix E for the evidence tables in full.

3.5.3 Evidence statements

For details of how the evidence is graded, see 'The guidelines manual'.

3.5.3.1 No evidence on the effectiveness of different models of care in the diagnosis of suspected anaphylaxis was identified.

3.5.4 Health economic modelling

This was not considered to be a health economic question.

3.5.5 Evidence to recommendations

Relative value of different outcomes	The GDG considered it important that there should be a defined referral pathway in place with the aim of preventing future reactions. As a result of their different needs, these pathways should be developed separately for children and for young people and adults. Where possible individuals should be referred to an age-appropriate service. However, in many instances the gap in provision will be for children. In these cases it is better for a child to be seen by an adult specialist allergist service than by a general paediatric team. Any referral needs to be to a service capable of confirming the anaphylactic reaction, identifying the cause of the reaction and developing an initial management plan.
Trade-off between clinical benefits and harms	The GDG considered that there were no potential harms from referring people to a specialist service.
Economic considerations	Not applicable
Quality of evidence	No evidence was identified.
Other considerations	The recommendations were based on the clinical expertise and experience of the GDG, who considered the recommendations to be accepted best practice.

3.5.6 Recommendations and research recommendations for models of care for the diagnosis of anaphylaxis

Recommendations

Recommendation 1.1.12 Each hospital trust providing emergency treatment for suspected anaphylaxis should have separate referral pathways for suspected anaphylaxis in adults (and young people) and children.

Research recommendations

See appendix B for full details of the research recommendations.

Research recommendation B5

For people who have experienced suspected anaphylaxis, what is the effect on health-related quality of life of (a) referral to specialist allergy services and (b) provision of adrenaline injectors, when compared with emergency treatment alone?

4 Notes on the scope of the guideline

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is given in appendix C.

5 Implementation

NICE has developed tools to help organisations implement this guidance (see www.nice.org.uk/guidance/CG134)'.

6 Other versions of this guideline

6.1 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from http://pathways.nice.org.uk/pathways/anaphylaxis

6.2 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG134/PublicInfo

For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk (quote reference number N2692).

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about anaphylaxis.

7 Related NICE guidance

Published

- Food allergy in children and young people. NICE clinical guideline 116 (2011). Available from www.nice.org.uk/guidance/CG116

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Pharmalgen for the treatment of venom allergy. NICE technology appraisal guidance.

8 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

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10 Glossary and abbreviations

Glossary

Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalised or systemic hypersensitivity reaction. It is characterised by rapidly developing, life-threatening problems involving: the airway (pharyngeal or laryngeal oedema) and/or breathing (bronchospasm with tachypnoea) and/or circulation (hypotension and/or tachycardia). In most cases, there are associated skin and mucosal changes[5].

Biphasic anaphylaxis

After complete recovery of anaphylaxis, a recurrence of symptoms within 72 hours with no further exposure to the allergen. It is managed in the same way as anaphylaxis.

Idiopathic anaphylaxis

Denotes a form of anaphylaxis where no identifiable stimulus can be found. All known causes of anaphylaxis must be excluded before this diagnosis can be reached.

Recurrence

A return of symptoms as part of the natural progress of a disease.

Suspected anaphylaxis

The diagnosis, prior to assessment by a specialist allergist, for people who present with symptoms of anaphylaxis.

In emergency departments a person who presents with the signs and symptoms of anaphylaxis may be classified as having a ‘severe allergic’ reaction rather than an ‘anaphylactic’ reaction. Throughout this guideline, anyone who presents with such signs and symptoms is classed as experiencing a ‘suspected anaphylactic reaction’, and should be diagnosed as having ‘suspected anaphylaxis’.

[5] Resuscitation Council (UK; 2008) Emergency treatment of anaphylactic reactions. Guidelines for healthcare providers.

Please see the NICE glossary (www.nice.org.uk/website/glossary/glossary.jsp) for an explanation of terms not described above.

Appendix A Contributors and declarations of interests

The Guideline Development Group

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A Short Clinical Guidelines Technical Team was responsible for this guideline throughout its development. It prepared information for the Guideline Development Group, drafted the guideline and responded to consultation comments.

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The Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring adherence to NICE guideline development processes. In particular, the panel ensures that stakeholder comments have been adequately considered and responded to. The panel includes members from the following perspectives: primary care, secondary care, lay, public health and industry.

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Declarations of interests

	Interest declared	Type of interest	Decisions taken
Prashant Kumar	Facilitates an allergy service at Sunderland Royal Hospital.	Personal pecuniary, non-specific	Declare and can participate in discussions.
	Chair of the Northern Paediatric Allergy Group (NPAG), an association of all the allergists or those with an interest in allergy in the Northern East. The aim of this group is to get uniform guidelines for the management of allergy.	Personal non-pecuniary	Declare and can participate in discussions on all topics.
	Organised a BSACI-endorsed allergy training day for primary care professionals in November 2010. This was supported by pharmaceutical companies (no personal financial interest) including Nutricia, Mead Johnson, ALK-Abello, MSD, Phadia and Glaxo.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics because the work was not specific to anaphylaxis.
	Delivered educational, non-promotional talks to GPs for companies making asthma treatment and treatment for allergic rhinitis. This may be classed as paid work. Companies involved were Glaxo, MSD, Schering Plough (now MSD), Orion Pharma.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics because the work was not specific to anaphylaxis.
Nigel Harper	Chaired a working party of the Association of Anaesthetists of Great Britain and Ireland, which considered some issues that will be relevant to the NICE GDG.	Personal non-pecuniary	Declare and can participate in discussions on all topics.
Sue Clarke	Given sponsorship to attend the BSACI Conference in Nottingham in July paid for by ALK-Abello. (This is the company that will be launching their new Adrenaline Injector in September.)	Non-personal pecuniary	Declare and can participate in discussions on all topics.
	The Anaphylaxis Campaign received an educational grant from Lincoln Medical (manufacturer of the Anapen) for a project I was involved in from December 2009 to July 2010. Education for Health have received a fee for a project which I was involved in during spring 2010 from Merck Sharp & Dohme Ltd. (MSD) (manufacturers of Singulair, used for some kinds of allergic disease, but not food allergy).	Non-personal pecuniary	Declare and can participate in discussions on all topics.
Lynette Williams	Received travel sponsorship from Novartis, ALK-Abello, GSK, Allergy Therapeutics Orion.	Personal non-pecuniary	Declare and can participate in discussions on all topics.
	Received speaker's fee for talks on allergy and asthma from ALK-	Personal pecuniary	Declare and can participate in discussions on all topics.

	Abello, GSK, Allergy Therapeutics.		
Mandy East	The Anaphylaxis Campaign receives funding from Lincoln Medical, ALK-Abello and Meda Pharmaceuticals. The National Allergy Strategy Group whom I also work with receives funding from ALK-Abello and Meda Pharmaceuticals. No money is given to me directly.	Non-personal pecuniary	Declare and can participate in discussions on all topics.
Pamela Ewan	Chair, National Allergy Strategy Group	Personal non-pecuniary	
Clare Taylor	No declarations		
Trevor Brown	No declarations		
Mathew Doyle	No declarations		
David Glaser	No declarations		
Nicola Mundy	No declarations		
Louise Sinnott	No declarations		

Appendix B List of all research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

B1 Mediators of anaphylactic reactions

Aside from mast cell tryptase, which other chemical inflammatory mediators offer potential as indicators of anaphylaxis?

Why this is important

Although mast cell tryptase is widely used to support the diagnosis of anaphylaxis, it is not universally suitable. Mast cell tryptase is not always elevated in children, when food is the allergen, or when the main severe feature is respiratory.

It is recommended that a cross-sectional study be carried out into the diagnostic accuracy of other potential chemical inflammatory mediators. The study should be conducted in both adults and children who have had a suspected anaphylactic reaction. The sensitivity and specificity of the proposed mediator should be compared against mast cell tryptase, using clinical assessment in conjunction with immuno-allergic study as the reference standard for both. The diagnostic accuracy of any mediator should be carried out for a range of potential allergens.

B2 The frequency and effects of biphasic reactions

What are the frequency, timing, severity and predictors of biphasic reactions in people who have received emergency treatment for anaphylaxis?

Why this is important

Limited evidence was found on the frequency, timing severity and predictors of biphasic reactions and the resulting effect of these on morbidity and mortality.

It is recommended that a UK-based prospective cohort study be conducted that follows patients up after emergency treatment for anaphylaxis.

The study should follow people up for 7 days after discharge from the emergency department. The aim is to collect data on the predictors (for example, the person's response to the initial treatment), the time to any reaction, the severity of any biphasic reaction and the effect of the biphasic reaction on morbidity and mortality.

B3 Length of observation period following emergency treatment for anaphylaxis

For how long should a person who has received emergency treatment for anaphylaxis be observed?

Why this is important

No studies were found that compared different observational periods or the effect of these on relevant patient outcomes.

It is recommended that a cluster randomised controlled trial is conducted for people who have received emergency treatment for anaphylaxis.

The interventions for the trial should be differing time periods of observation, within the secondary care setting, ranging from 1 hour to 24 hours after symptom resolution of the index reaction. Patients should then be followed up for 7 days following the end of the observational period to determine if a biphasic reaction has occurred and the effects of any reaction. The aim is to determine whether differing periods of observation have a detrimental effect on morbidity and mortality and to gather information about resource use.

B4 Prevalence of anaphylactic reactions and related outcomes

What is the annual incidence of anaphylaxis and its related outcomes within the UK?

Why this is important

Limited evidence exists on the annual incidence of anaphylactic reactions and their associated outcomes within the UK.

It is recommended that a prospective observational study be conducted that records the annual incidence of anaphylactic reactions within the UK.

The overall number of anaphylactic reactions that occur in adults and children should be recorded and these should be classified into those that are first-time reactions, recurrent reactions or biphasic reactions. A clear, pre-defined, definition of what constitutes an anaphylactic reaction should be used, in order to avoid the misclassification of milder reactions. Data should also be collected on any emergency treatment that was delivered (by a clinician, use of an adrenaline injector) and the associated outcomes (morbidity, mortality, adverse events). Data should also be collected on any previous treatment received, such as that from a specialist allergy service or the provision of adrenaline injectors.

B5 Effect of specialist services on health-related quality of life.

For people who have experienced suspected anaphylaxis, what is the effect on health-related quality of life of (a) referral to specialist allergy services and (b) provision of adrenaline injectors, when compared with emergency treatment alone?

Why this is important

The GDG believed that referral to specialist services and/or the provision of adrenaline injectors was likely to provide day-to-day HRQoL benefit for people who have experienced suspected anaphylaxis, as a result of decreased anxiety and ongoing support. However, the health economic model relied on GDG opinion alone to quantify this benefit. Future economic analyses would be greatly improved by a reliable demonstration of this effect and an estimate of its magnitude. It is recommended that data are collected using validated measure(s) of HRQoL, including EQ-5D.

Appendix C Guideline scope

See separate file.

Appendix D How this guideline was developed

See separate file.

Appendix E Evidence tables

See separate file.

Appendix F Full health economic report

See separate file.

Appendix G Technical assessment report (sections 3.3.2 and 3.3.4)

See separate file.