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Abstract

A systematic review and cost-effectiveness analysis of specialist services and adrenaline auto-injectors in anaphylaxis

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Background: Anaphylaxis is a severe, life-threatening generalised or systemic hypersensitivity reaction with high mortality. Specialist services (SSs) are believed to reduce anaphylaxis recurrence and improve use of adrenaline injectors (AIs), which can reduce mortality if used correctly and in time.

Objectives: To review the evidence on which persons are at high risk of anaphylactic episodes, the effects of history-taking (including signs, symptoms and physical examination) for anaphylaxis, and when (suspected) patients should be referred. To assess the cost-effectiveness of SS compared with standard care (SC) with or without prescription of AIs.

Data sources: In order to assess the clinical effectiveness, 10 databases [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), Science Citation Index (SCI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, from inception up to March 2011] were searched without data restriction in order to identify relevant studies [randomised controlled trials (RCTs), controlled clinical trials, observational studies, prognostic studies using a multivariate model] written in English.

Review methods: Standard review methods were applied for the assessment of clinical effectiveness. A Markov model, validated by clinical experts, was constructed, which modelled anaphylaxis according to trigger: either food, drug, insect or idiopathic. Anaphylaxis mortality was modelled as a function of time to die and time for emergency response. Probabilistic sensitivity analysis on key parameters was performed.

Results: From the systematic review, 11,058 references were identified by the searches for studies assessing the clinical effectiveness. In total, 107 papers were obtained, and five prospective observational studies, including 1725 patients, were included. These studies estimated the risk of recurrence to be between 30% and 42.8%. In children (<12 years), an overall recurrence of 27% was reported, with food being the most frequent allergen (71%). From the cost-effectiveness analysis (CEA), SC with injectors was dominated by SS with or without injectors. SS with no injectors would be cost-effective if the threshold for a quality-adjusted life-year (QALY) was greater than about £740 and with injectors would be cost-effective if the threshold was >£1800. These results were robust to all sensitivity analyses except at relatively extreme values of a small number of parameters.

Limitations: Limitations of the study include the low yield from the systematic review; in particular there were no good-quality studies of either SSs or AI effectiveness. This implied a great reliance on expert opinion in the CEA. However, this was appropriately addressed using sensitivity analysis.

Conclusions: Only five observational studies assessing clinical effectiveness were identified. Owing to the lack of good data to inform the effectiveness of anaphylaxis intervention, we recommend considerations of RCTs or at least well-designed observational studies of the components of care in SSs. The results of the CEA showed that SS with AIs was cost-effective at a threshold of £20,000 per QALY. More well-designed prospective studies on the effectiveness of SSs are needed to confirm these findings.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

AI	adrenaline injector
BMJ	*British Medical Journal*
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DAM	decision-analytic model
ED	emergency department
GDG	Guideline Development Group
GIN	Guidelines International Network
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IgE	immunoglobulin E
NICE	National Institute for Health and Care Excellence
ODA	optimal discriminant analysis
PICO	population, intervention, comparison, outcome
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SC	standard care
SS	specialist service
VIT	venom immunotherapy
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

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).

There is considerable geographic variation in both practice and service provision for anaphylaxis, specifically in reviews after emergency treatment for anaphylaxis and decisions about when and whether or not to refer to a specialist allergy clinic [specialist service (SS)] {'. . . 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' [p. 9, National Institute for Health and Care Excellence (NICE) guideline CG134, www.nice.org.uk/nicemedia/live/13626/57474/57474.pdf]}. There are professional guidelines on the emergency treatment and management of anaphylaxis, but there is currently no relevant national guidance for England and Wales on assessment after the event to confirm an anaphylactic episode or on the decision to refer after emergency treatment.

There are approximately 20 anaphylaxis deaths reported each year in the UK, although this may be a substantial underestimate. There are observational data that the risk of death is increased by delayed use of adrenaline. In order to reduce the delay, adrenaline injectors (AIs) are often prescribed following anaphylaxis, but there is a perception that they are often not used in time or correctly.

Objectives

For the NICE clinical guideline CG134 'Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode', we, as the Technology Assessment Group, were asked to address six questions:

1. In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?
2. What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause?
3. What are the effects of providing adrenaline auto-injectors, including by whom?
4. After assessment, when should referral take place?
5. What is the cost-effectiveness of referral to specialist allergy clinics for the diagnosis of anaphylaxis and for the prevention of future episodes and the reduction in morbidity and mortality from future episodes?
6. What is the cost-effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis, including the cost implications of training in the use of the auto-injectors?

Questions 1–4 aimed to shed light on clinical aspects of anaphylactic episodes, whereas questions 5 and 6 addressed the cost-effectiveness of diagnosis, prevention and treatment of anaphylaxis.

Methods

Clinical aspects (questions 1–4)

The search strategies for the review questions were developed by the information specialist with advice from the systematic review team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free-text terms. The strategies were run across 10 databases [Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), NHS Economic Evaluation Database (NHS EED), Science Citation Index (SCI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, from inception up to March 2011] with no date restrictions imposed on the searches.

Studies [randomised controlled trials (RCTs) or non-RCTs, observational studies, and prognostic studies that have included a multivariable analysis], published in English, which focused on patients who received emergency treatment for suspected anaphylaxis or severe allergic reactions, were eligible for inclusion if they reported history-taking, physical examination, provision of adrenaline auto-injectors or referral to specialist allergy clinics. Relevant clinical outcomes were subsequent episodes, morbidity and mortality, as well as the impact on the treatment plan and test failure rates. There was no limitation regarding age of patients and setting.

Economic aspects (questions 5 and 6)

In order to answer both questions 5 and 6, an objective of the study was constructed to assess the cost-effectiveness of referral to specialist allergy clinics (SSs) as opposed to standard care (SC), i.e. no referral after the acute event, with or without prescription of AIs for the treatment of anaphylaxis.

In order to achieve this objective, first a review of the extant cost-effectiveness analysis (CEA) literature was conducted, which revealed that the cost-effectiveness of SS had never been estimated before. One study had examined AI, but only in the general allergic population as opposed to those who have had anaphylaxis, and it had not estimated quality-adjusted life-years (QALYs).

Therefore, informed by expert opinion from the Guideline Development Group, a Markov model was constructed to model the possibility of recurrence over a lifetime in each of the subgroups by cause of anaphylaxis: insect, food, drug and idiopathic origin. It modelled the effect of SSs in terms of rate reduction via a mechanism that depended on the trigger, assuming that all patients had anaphylaxis and that trigger was identified with certainty. AI (prescription of two injectors) effect was modelled as having an effect only on mortality due to recurrence. Of the five studies retrieved to answer questions 1–4, only one, an Australian observational study on risk of recurrence, was used to inform the model. All other parameter estimates were informed by a review of evidence based on clinical guidelines and expert opinion.

Results

Clinical aspects (questions 1–4)

The searches of electronic searches yielded in 11,058 references. After screening of titles and abstracts, 10,951 references were excluded. The remaining 107 references were obtained and the full texts screened. Five studies were included, none of which was a RCT. Another 60 studies were highlighted as possibly relevant for the background and/or the CEA. All five included studies were prospective observational studies reporting on risk of recurrence. The studies, conducted in five countries (Australia, Germany, Italy, Spain and the USA), included 1725 patients overall.

Risk of recurrence was estimated to be between 30% and 42.8%. One study suggested the rate of a third event to be 5.2% with a higher risk of recurrence for women [relative risk (RR) 2.14, 95% confidence interval (CI) 1.17 to 3.9]. In children of < 12 years, an overall recurrence of 27% was reported, with food being the most frequent allergen (71%). One larger study (432 patients) reported serious recurrences in 45 patients (10.4%), of whom 18 (40%) received adrenaline.

Economic aspects (questions 5 and 6)

The results showed that, in the base case of a lifetime horizon, discount rate of 3.5%, SS with AI had an incremental cost-effectiveness ratio (ICER) of about £1800 (model run probabilistically or deterministically, i.e. all parameters set at expected value) and, therefore, would be cost-effective according to a threshold of no less than this figure. Any SC strategy (with or without AI) was dominated, i.e. found to be less effective and more costly than another strategy. SS with no AI would be cost-effective only below a threshold of about £740. The cost-effectiveness acceptability curve also revealed that above a willingness to pay of about £2000, SS plus AI was also the most likely (highest probability) to be cost-effective.

Given the complexity of the model and much uncertainty there was in many parameters, extensive sensitivity analysis in the form of threshold analyses was performed. This revealed that variation in most parameters would not change the strategy that would be cost-effective. Indeed, only relatively extreme values for rate of food caused anaphylaxis following SS could cause a change to SC. Similarly, only relatively extreme values for the cost of injector, probability of dying with the injector or utility improvement factor (essentially the proportion of the utility decrement due to living with the risk of anaphylaxis that would be restored as a result of prescription of an injector) could cause a change to SS with no injector. One possible exception was that SS no AI might be cost-effective below a probability of correct use of AIs of 0.77, assuming no utility increment with AIs (e.g. due to reassurance).

Conclusions

The results of the systematic review revealed only five studies that directly addressed any of the research questions in terms of history-taking, physical examination, provision of adrenaline auto-injectors or referral to specialist allergy clinics for those with anaphylaxis. None of these studies was a RCT.

The results of the CEA showed that SS with AI was cost-effective at a threshold of £20,000 per QALY. However, given the lack of RCTs, the model had to be informed by observational studies and expert opinion.

Given that the results that both referral to a SS and prescription of AIs are likely to be cost-effective and that this study has been used to inform a NICE guideline, it does potentially have important implications for policy. The guideline was published in December 2011.

Research recommendations

The lack of good data to inform the effectiveness of anaphylaxis intervention means that we recommend consideration of RCTs or at least well-designed observational studies of the components of care in SSs. These components include all of those that formed the CEA model, including AIs, trigger avoidance measures, venom immunotherapy and idiopathic anaphylaxis treatment.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

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).

There is considerable geographic variation in both practice and service provision for anaphylaxis, specifically in reviews after emergency treatment for anaphylaxis and decisions about when and whether or not to refer to a specialist service (SS). There are professional guidelines on the emergency treatment and management of anaphylaxis, but there is currently no relevant national guidance for England and Wales on assessment after the event to confirm an anaphylactic episode or on the decision to refer after emergency treatment.

There are approximately 20 anaphylaxis deaths reported each year in the UK, although this may be a substantial underestimate. There are observational data that the risk of death is increased by delayed use of adrenaline. In order to reduce the delay, adrenaline injectors (AIs) are often prescribed following anaphylaxis, but there is a perception that they are often not used in time or correctly.

Chapter 2 Definition of the decision problem

For the National Institute for Health and Care Excellence (NICE) clinical guideline CG134 'Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode', we, as the Technology Assessment Group, were asked to address six questions:

1. In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?
2. What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause?
3. What are the effects of providing adrenaline auto-injectors, including by whom?
4. After assessment, when should referral take place?
5. What is the cost-effectiveness of referral to specialist allergy clinics for the diagnosis of anaphylaxis and for the prevention of future episodes and the reduction in morbidity and mortality from future episodes?
6. What is the cost-effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis including the cost implications of training in the use of the auto-injectors?

Questions 1–4 are addressed in *Chapter 3* and questions 5 and 6 are addressed in *Chapter 4* of this report.

Chapter 3 Assessment of clinical effectiveness

Note: this chapter is reproduced from the original project protocol. See also *Chapter 2* and *Chapter 4, Methods of cost-effectiveness analysis*.

Methods for reviewing effectiveness

Research questions

This section addresses the four research questions:

1. In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?
2. What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause?
3. What are the effects of providing adrenaline auto-injectors, including by whom?
4. After assessment, when should referral take place?

Identification of studies

The evidence reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in 'The guidelines manual' (2009).[1] The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group (GDG) and Short Clinical Guidelines Technical Team.

The search strategies for the review questions were developed by the information specialist with advice from the systematic review team. Structured questions were developed using the PICO (population, intervention, comparison, outcome) model and translated into search strategies using subject heading and free-text terms. The strategies were run across a number of databases, with no date restrictions applied to the searches.

The NHS Economic Evaluation Database (NHS EED) was searched for economic evaluations. A search filter for economic evaluations was used on bibliographic databases. There were no date restrictions applied to the searches.

The searches were undertaken between 17 January and 17 March 2011.

Scoping searches

Scoping searches were undertaken in January 2011 using the following websites and databases (listed in alphabetical order) shown in *Table 1*; browsing or simple search strategies were used. The search results were used to provide information for scope development and project planning.

Main searches

The following sources were searched for the topics presented in the sections below:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) [Centre for Reviews and Dissemination (CRD)]
- Health Technology Assessment database (HTA) (CRD)
- NHS Economic Evaluation Database (NHS EED) (CRD)
- Science Citation Index (SCI) (Web of Science)

TABLE 1 Sources of systematic reviews, economic evaluations and guidance

Systematic reviews/economic evaluations	Guidance/guidelines
Cochrane Central Register of Controlled Trials (CENTRAL)	Guidelines International Network (GIN)
Cochrane Database of Systematic Reviews (CDSR)	National Guidelines Clearinghouse
Database of Abstracts of Reviews of Effects (DARE)	
Health Technology Assessment database (HTA)	
NHS Economic Evaluation Database (NHS EED)	

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost)
- EMBASE (OvidSP)
- MEDLINE (OvidSP)
- MEDLINE In-Process & Other Non-Indexed Citations and MEDLINE Daily Update (OvidSP).

Identified references were downloaded in EndNote X4 software (Thomas Reuters, CA, USA) for further assessment and handling.

Inclusion and exclusion criteria

Participants
Adults, young people and children who received emergency treatment for suspected anaphylaxis or severe allergic reactions (that may have developed into anaphylaxis without treatment).

Setting
Relevant settings were primary, secondary or tertiary care.

Interventions/diagnostic assessments
- History-taking.
- Physical examination.
- Provision of adrenaline auto-injectors.
- Referral to specialist allergy clinics.

Comparators
- Elements of history-taking compared with each other and compared with not considering those elements.
- Elements of physical examination compared with each other and compared with not considering these elements.
- Provision of auto-injectors by different health-care professionals.
- No provision of adrenaline auto-injectors.
- Referral to other specialists.
- No referral.

Outcomes
Any or all of the following outcomes were considered:

- impact of testing/predictors on clinical outcome, (e.g. subsequent episodes, morbidity, mortality), correlations between tests and clinical outcomes
- impact of adrenaline auto-injectors on clinical outcome (e.g. subsequent episodes, morbidity, mortality)
- impact of referral on clinical outcome (e.g. subsequent episodes, morbidity, mortality)

- indeterminacy (test failure rate)
- impact of testing/predictors on treatment plan (e.g. referral or not or to whom), where information on the appropriateness of the final treatment plan is also reported.

For included studies reporting any of the above outcome measures, the following outcomes were also considered if reported:

- acceptability of tests to patients
- adverse events associated with testing.

Study designs

The following types of studies were included:

- randomised controlled trials (RCTs) or non-RCTs
- observational studies reporting change to treatment plan or clinical outcome subsequent to intervention or testing
- prognostic studies that have included a multivariable analysis (evaluating risk factors or signs in an analysis that includes other relevant factors or signs, rather than an unadjusted correlation).

The following study/publication types were excluded:

- pre-clinical, animal studies
- reviews, editorials, and opinion pieces
- case reports
- studies reporting only technical aspects of the test
- studies with <20 participants.

Data abstraction strategy

Included studies were summarised using evidence tables for prognostic studies (see appendix K3 of the NICE guidelines manual).[1] These tables can be found in *Chapter 3 (see Results)*. Extraction of one reviewer was checked by another. Furthermore, Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings tables[2] were prepared. Any disagreement was discussed with a third reviewer.

Critical appraisal strategy

Quality and strength of evidence of included studies was assessed using the methodology checklist for prognostic studies (see appendix J of the NICE guidelines manual).[1] These tables can be found in *Appendix 2*. In addition, quality was assessed using the GRADE methodology.[2]

Methods of data synthesis

Not applicable.

Results

Quantity and quality of research available

The searches of electronic searches yielded in 11,058 references. After screening of titles and abstracts, 10,951 references were excluded. The remaining 107 references were obtained and the full texts were screened. Five studies were included, with another 60 studies highlighted as possibly being relevant for the background and/or the cost-effectiveness analysis (CEA). A flow chart of the screening process is presented in *Figure 1*.

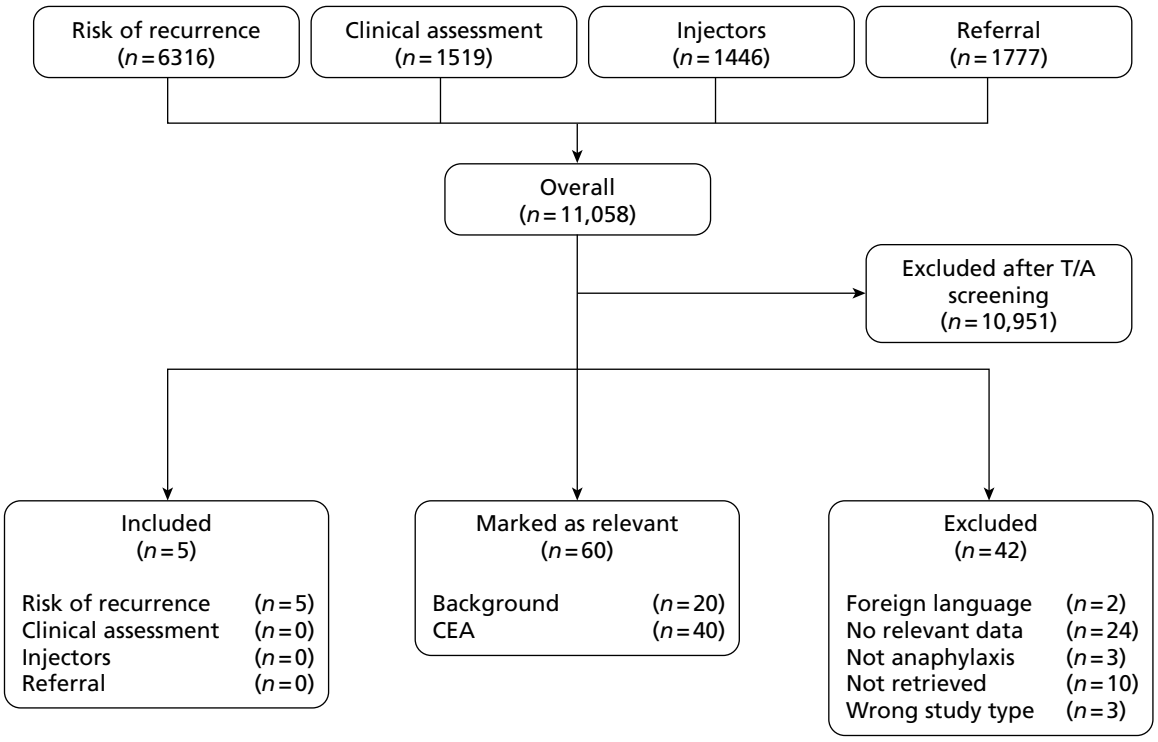

FIGURE 1 Flow chart of study identification. T/A, title and abstract.

Assessment of clinical effectiveness

All five included studies were prospective observational studies reporting on risk of recurrence.[3–7] The studies, conducted in five countries (Australia, Germany, Italy, Spain and the USA), included 1725 patients overall.

The risk of bias using the NICE methodology checklist for prognostic studies[1] was rated as low for three studies[3,4,7] or medium (two studies)[5,6] (*Table 2*). Two of the studies were published only as abstracts, which limited the amount of methodological details reported in these studies.[4,6] Overall, problems included unclear definition of recurrence (three studies),[4,5,7] unclear patient selection (one study),[3] insufficient details on role of funding source (one study)[5] and missing details on included patients (one study).[6] The quality assessment is presented in *Appendix 2*.

Using the GRADE methodology,[2] quality of evidence extracted from the included studies was rated as 'very low'. It should be noted that using the GRADE approach quality of evidence from observational studies is initially rated as 'low'. During further assessment, certain areas can lead to upgrading or downgrading of the quality. Application of the GRADE methodology to the included studies is shown below (see *Table 4*). Each row of the table reports on outcomes that are addressed by included studies, and highlights problems with any of the included studies in relation to each outcome. Footnotes identify specific threats to validity identified. As can be seen in the table, the main reasons for downgrading of included evidence were missing details on blinding, as well as size of studies, i.e. number of included participants. Readers should note that the different systems of identifying bias (NICE methodology checklist for prognostic studies vs GRADE) yield slightly different conclusions on the levels of threat to validity and therefore the quality of studies is described differently (see *Tables 2* and *4*).

All included studies reported the number of patients with recurrent anaphylactic episodes. Risk of recurrence was estimated to be between 30% and 42.8%. Overall, 497 of 1386 patients (35.9%) had a recurrent anaphylactic episode (see *Table 4*). One study suggested the rate of a third event to be 5.2%, with a higher risk of recurrence for women [relative risk (RR) 2.14, 95% confidence

interval (CI) 1.17 to 3.9].[4] In children of < 12 years, an overall recurrence of 27% was reported with food being the most frequent allergen (71%).[5] One larger study (432 patients) reported serious recurrences in 45 patients (10.4%) of whom 18 (40%) received adrenaline.[7] This study also presented findings on mortality and reported no deaths.[7] Another study presented results for sex, age, and race (see *Table 4* for details).[4]

Characteristics and findings of the included studies are presented below. *Table 2* shows characteristics of the five included studies. The findings of these studies are presented in *Tables 3* and *4*.

No studies that fulfilled inclusion criteria for objectives 2–4 were identified.

Summary

Overall, five prospective observational studies reporting on risk of recurrence were included.[3–7] No studies were found for the questions on history-taking, adrenaline auto-injectors, and referral.

The included studies reported a recurrent anaphylactic episode for 497 of 1386 patients (35.9%), indicating that recurrent episodes are relatively common for anaphylactic patients (see *Table 4*). Findings of single studies suggested that women have a higher risk of recurrence. Around one-quarter (27%) of recurrences in children of < 12 years are caused by food.

Limitations and implications for future research

Although a comprehensive search was undertaken to identify relevant studies (see *Quantity and quality of research available*), only five studies were included (see *Assessment of clinical effectiveness*). All of these studies are observational studies with low or medium risk of bias assessing the risk of recurrence. The studies were relatively small (1725 patients) and assessed the risk of recurrence in various patient groups. This should be taken into account when formulating recommendation based on these studies.

No studies addressing any of the other clinical research questions in terms of history-taking, physical examination, provision of adrenaline auto-injectors or referral to specialist allergy clinics for those with anaphylaxis were identified.

Lack of good data to inform the effectiveness of anaphylaxis interventions means that RCTs or at least well-designed observational studies of the components of care in SSs should be conducted. Ideally, these should report findings based on large numbers of participants, if possible divided into relevant subgroups.

TABLE 2 Characteristics of included studies

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
Cianferoni 2004[3]	Cianferoni A, Novembre E, *et al*. Anaphylaxis: a 7-year follow-up survey of 46 children. *Ann Allerg Asthma Immunol* 2004;**92**:464–8	Observational retrospective	Low risk of bias, but unclear how patients were selected	Recurrence defined as the presence of another anaphylaxis episode: at least two of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnoea, and urticaria/angio-oedema) within 2 hours after exposure to one of the most probable causative agents Defined risk factors for recurrence: history of atopic dermatitis, current urticaria/angio-oedema, history to sensitivity to one food allergen	7 years (SD 1 year, range 5–8.6 years)	N/R
Decker 2008[4]	Decker KW, Bellolio MF, *et al*. Recurrent anaphylaxis events in patients presenting to the emergency department over a 10-year period. *Ann Emerg Med* 2008;**51**: 214	Observational prospective	Low risk of bias, but no definition of recurrence given	No details provided	Mean 1.1 years (range 7 days to 13 years)	N/R
Mehl 2005[5]	Mehl A, Wahn U, *et al*. Anaphylactic reactions in children: a questionnaire-based survey in Germany. *Allergy* 2005;**60**:1440–5	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 episode, 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 episode	1 year (patients identified over a period of 12 months retrospectively)	Industry: InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany ('financial support')

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
Múgica Garcia 2010[6]	Múgica Garcia M, Tejedor Alonso M, *et al*. (2010). A study of the recurrence of anaphylaxis. *Allergy: European Journal of Allergy and Clinical Immunology*. 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London, UK. Conference Publication: (various pages). 65 (p. 587), 2010. Published June 2010	Observational retrospective	Medium risk of bias as only 58.7% of previous cohort was included and no details on age, sex, weight and ethnicity were reported	Recurrence defined as any new episode of anaphylaxis, irrespective of the cause of the first episode 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 episode and the recurrence	N/R	N/R
Mullins 2003[7]	Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 2003;**33**:1033–40	Observational prospective	Low risk of bias, but no definition of recurrence given	Recurrence presented as proportion of patients relapsing Rate of recurrence per 100 patient-years of observation: calculated by dividing the cumulative length of observation by the number of recurrences involving that trigger	2.2 years	N/R

N/R, not reported; SD, standard deviation.

TABLE 3 Findings of included studies

Study	Setting	No. of patients	Patient characteristics	Results
Cianferoni 2004[3]	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 two of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnoea, and urticaria/angio-oedema) within 2 hours after exposure to one of the most probable causative agents	Diagnosed anaphylaxis. Mean age 14 (SD 4.92, range 7–26) years Age at first episode: 5.8 (SD 4.9, 1–18) years 61% male. No details on weight and ethnicity Aetiology: food 19.5% (9/46), exercise 4.4% (2/46), drug 2.2% (1/46) and idiopathic 4.4% (2/46)	Risk of recurrence: 30% (14/46)
Decker 2008[4]	Primary care, USA	211 (visiting an ED) Diagnosed anaphylaxis criteria from the National Institutes of Health/Food and Allergy and Anaphylaxis network	Mean age: 29.3 (SD 18.2) years. 44.1% male. No further details	Second event in 45/211 (21.3%). Median time of presentation: 395 days (range 7 days to 13 years). Third event in 11/211 (5.2%) Risk of recurrence for women higher (RR 2.14, 95% CI 1.17 to 3.9). No difference in age ($p = 0.535$) or race ($p = 0.743$) for a subsequent event
Mehl 2005[5]	Primary care, Germany	103 children (<2 years) Inclusion: reported accidental anaphylactic reactions occurring during 12 months in infants and children of <12 years of age. Reports reviewed individually by two paediatric allergologists Exclusion: reported cases excluded if the reported episode was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not <12 years	Median age 5 years (range 3 months to 12 years) 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[a] 4% (4/103) and 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) and other[a] 25% (15/59)	'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 years, SD 3 years) • SIT, 'significantly older' (mean 9.8 years, SD 1.9 years) • Venom, 'patients significantly older' (mean 7.6 years, SD 3.2 years) 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 episode(s) in medical history 50% (14/28)

Study	Setting	No. of patients	Patient characteristics	Results
Múgica Garcia 2010[6]	Primary care, Spain	933 (original cohort of 1590) Presented anaphylaxis and were followed in allergy unit (no further details)	Diagnosed anaphylaxis. Mainly urban community. No details on age, sex, weight and ethnicity	Overall risk 325/933 (34.8%) Same type as first episode: • Latex: 72.7% • Food: 38.8% • Unknown: 32.9% • Hymenoptera venom: 33.3%
Mullins 2003[7]	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 (SD 19.5, range 1–82) years 48% male No details on weight and ethnicity First episode during study course/before study: 71%/29%	130/304 (42.8%) have experienced 386 episodes of recurrent symptoms (median 2, range 0–18) Risk of overall recurrence: 57/100 patient-years; risk of severe recurrence: 10/100 patient-years Risk factors for recurrence: exercise and idiopathic cause, female sex No deaths Serious recurrences: 10.4% (45/432); had adrenaline: 40% (18/45) No serious recurrences: 19.7 (85/432); had adrenaline: 1.2% (1/85)

ED, emergency department; SD, standard deviation; SIT, specific immunotherapy.

a 'Less than or equal to two cases per allergen' when referring to a category of allergen called 'other'.

TABLE 4 Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings

Quality assessment							Summary of findings	
							No. of patients with recurrent anaphylactic episodes (unless stated otherwise)	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	*n/N*	Quality
No. of patients with recurrent anaphylactic episodes (follow-up mean 1–7 years[a])								
Five (all included studies[3–7])[b]	Observational studies[c]	Serious[d]	No serious inconsistency	No serious indirectness	Serious[e]	None	497/1386 (35.9%)	⊕000 VERY LOW
Mortality: no. of patients who died owing to anaphylactic reactions (follow-up mean 2.2 years)								
One[7]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/304 (0%)[g]	⊕000 VERY LOW
No. of patients with second recurrent anaphylactic episodes (follow-up mean 1.1 years)								
One[4]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	Serious[h]	None	45/211 (21.3%)[i]	⊕000 VERY LOW
No. of patients with third recurrent anaphylactic episodes (follow-up mean 1.1 years)								
One[4]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	Serious[h]	None	11/211 (5.2%)	⊕000 VERY LOW
Sex comparison for anaphylactic recurrent episodes (follow-up mean 1.1 years)								
One[4]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[h,j]	None	RR 2.14 (95% CI 1.17 to 3.9)[k]	⊕000 VERY LOW

Quality assessment							Summary of findings	
							No. of patients with recurrent anaphylactic episodes (unless stated otherwise)	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	*n/N*	Quality
Age comparison for anaphylactic recurrent episodes (follow-up mean 1.1 years)								
One[4]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[h,j]	None	$p = 0.535$[i,l]	⊕000 VERY LOW
Race comparison for anaphylactic recurrent episodes (follow-up mean 1.1 years)								
One[4]	Observational studies	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[h,j]	None	$p = 0.743$[i,m]	⊕000 VERY LOW

Settings: primary care (Australia, Germany, Italy, Spain, USA).

a Múgica Garcia 2010:[6] length of follow-up not reported.

b Cianferoni 2004,[3] Decker 2008,[4] Mehl 2005,[5] Múgica Garcia 2010,[6] Mullins 2003.[7]

c Age of participants, mean (years): 14 (Cianferoni[3]), 27.4 (Mullins[7]), 29.3 (Decker[4]); 5 (Mehl,[5] median); not reported (Múgica Garcia[6]).

d Details on blinding of participants, investigators and outcome assessors missing (four studies). No details on sex, age, length of follow-up, definition of recurrence unclear (one study).

e Low number of patients (<300 patients) in two studies.

f Details on blinding of participants, investigators and outcome assessors missing.

g Study reported that there were no deaths.

h Total number of patients: $n = 211$; studies with $n < 300$ were considered small.

i Median time of presentation with the second episode was 395 days (range 7 days to 13 years).

j Limited data reported on age and race.

k Study stated: 'Women were at higher risk of recurrence than men: RR 2.14 (95% CI 1.17 to 3.9); risk difference 0.15 (95% CI 0.04 to 0.26); $p = 0.009$.'

l Study stated: 'There was no difference in age ($p = 0.535$).'

m Study stated: 'There was no difference in race ($p = 0.743$) for a subsequent event.'

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A search strategy was designed in order to retrieve any economic evaluation or cost study in the population of allergy or anaphylaxis (refer to *Appendix 1* for how this was applied to each database). Forty papers were retrieved from title and abstract screening and three met the inclusion criteria for design and population.

Two studies[8,9] were published that reported on economic evaluations in the form of decision-analytic models (DAMs) of the use of AIs ($n = 2$) in a general allergy population[8] and in patients with a mild venom anaphylaxis[9] in the USA. Another American study evaluated the treatment and its related costs in patients with idiopathic anaphylaxis.[10] All studies (*Table 5*) reported the costs in US dollars (US$). To assess the quality of reporting of these economic evaluations the *British Medical Journal* (BMJ) checklist was used, including 35 items (http://resources.bmj.com/bmj/authors/checklists-forms/health-economics). The BMJ checklist showed that 11 out of 35 criteria were satisfactorily reported for the study by Krasnick *et al.*,[10] and 18 out of 35 for the study reported by Shaker 2007.[9] The study published by Desai and Carroll 2009[8] was reported only as a congress abstract, which unsurprisingly resulted in many missing sections of the BMJ checklist (30 out of 35). Full details are in *Appendix 4*.

In the following paragraphs the details of the three studies are presented.

Krasnick et al. *1996*

This study[10] was designed to determine the efficacy of a specialist treatment in a University Allergy-Immunology Division using oral corticosteroids, antihistamines, and sympathomimetics for patients with idiopathic anaphylaxis. A total of 225 patients, diagnosed with idiopathic anaphylaxis and treated in one university hospital from 1971 to 1990, were retrospectively reviewed. The costs of both emergency care [physician fees, medications (intravenous corticosteroids, subcutaneous adrenaline and intramuscular diphenhydramine), pulse oximetry and cardiac monitoring] and hospitalisation (general medical floor hospital admission and intensive care unit admission with and without need of intubation and mechanical ventilation) were estimated on the basis of costs of services at Northwestern Memorial Hospital, Chicago, IL, USA, during the year 1995 (no details on unit costs were reported). Optimal discriminant analyses (ODAs) were used to determine whether or not the treatment protocol made a significant decrease in hospital costs for four subgroups of patients with idiopathic anaphylaxis. Significant decreases in emergency room visits occurred for three of the four subgroups of patients with idiopathic anaphylaxis. Significant decreases in the number of hospitalisations ($p < 0.022$) and intensive care unit admissions ($p < 0.009$) occurred for the patients with idiopathic anaphylaxis with generalised symptoms (two subgroups). Overall, there were 165 emergency room evaluations, 17 hospitalisations and 18 intensive

TABLE 5 Summary of economic evaluations on anaphylaxis

Study	Design	Population	Comparators
Krasnick *et al.* 2010[10]	Cost description	Idiopathic anaphylaxis	Before AI implementation compared with after AI implementation
Shaker 2007[9]	DAM for CEA	Children with mild venom anaphylaxis	Treatment of mild venom anaphylaxis with AI compared with treatment of mild venom anaphylaxis without AI use
Desai and Carroll 2009[8]	DAM	Users of AI	Conventional AI [EpiPen (Meda Pharmaceuticals Ltd, Bishop's Stortford, UK) compared with a new AI device (Intellijject, Intellijject Llc., Richmond, VA, USA)]

care unit admissions (five admissions requiring intubation) before patients received the specialist treatment at a cost of US$225,000. There were 51 emergency room visits, three hospitalisations, and no intensive care unit admissions after patients received the SS at an estimated cost of US$40,260, producing a saving of US$184,740.

Shaker 2007

This study[9] was designed to evaluate the cost-effectiveness of the prophylactic self-injectable adrenaline in mild childhood venom anaphylaxis from a societal perspective, although the only cost data included in the model were the market costs of an AI (US$50 per year). A Markov model evaluated two scenarios: one using an AI and another not using an AI for the treatment of venom anaphylaxis. The base case in each scenario was represented by a 6-year-old child. The year '2007' was used as the baseline cost year and a discount rate of 3% was used for future costs and years. Literature sources were used to estimate mortality but the model assumed that all deaths would be prevented by the AI, regardless of time between trigger and death or success in use. One-way sensitivity analysis was performed of the following parameters: age, fatality rates of anaphylaxis and duration of use of AI after prescription.

The main findings were as follows: the incremental cost of prophylactic AI for mild childhood venom anaphylaxis was US$469,459 per year of life saved and US$6,882,470 per death prevented when evaluated at a 40-year time horizon. The sensitivity analysis revealed that the use of AI might become cost-effective at US$97,146 per life-year saved only if the annual fatality rate exceeded 2 per 100,000 persons at risk. The conclusion of this study was that the use of prophylactic AI to prevent fatalities in children with mild venom anaphylaxis is not cost-effective if the annual venom-associated fatality rate is <2 per 100,000 persons at risk. The source of financial support of this study was not reported.

Desai and Carroll 2009

This study[8] compared the costs and consequences of using an established device (probably the EpiPen) compared with a novel device (Intellijject) for treatment of a uniphasic anaphylactic reaction. The decision tree model evaluated the two scenarios from a health-payer perspective, but no information was provided on the baseline cost year, length of the time horizon and a discount rate used. The consequences included recovering without visiting the emergency department (ED), ED use and hospitalisations. The costs included in the model were costs of device use, ED use and hospitalisations. Data were obtained from literature, an online query tool for health care cost (HCUPnet) and clinical study data of the company that developed the new AI (Intellijject Inc., Richmond, VA, USA). One-way sensitivity analyses were conducted for patients' probabilities of carrying the device, using it correctly and of recovery and death after using the device incorrectly. The base-case results per 100 patients indicate that the new device would lead to more patients recovering without visiting the ED (57 vs 35), similar rates of ED use without hospitalisation (7) and fewer hospitalisations (2 vs 4). The results also indicated higher device costs (US$15,837 vs US$6291) and the same ED use costs (US$9375), but lower costs for hospitalisations (US$15,303 vs US$30,606), leading to lower total costs of the new device (US$40,515 vs US$46,272) (no statistical analyses on outcomes and costs were reported). Sensitivity analyses indicated that the new device would have lower total costs and lead to better consequences under most tested assumptions. The authors stated that the assumed price premium (not reported) of the new device provided lower total costs, and a higher recovery rate, as well as fewer hospitalisations.

Summary

None of these studies is useful in directly addressing the questions regarding SSs. However, the study by Krasnick *et al.*[10] does provide useful data in terms of the time to remission in idiopathic anaphylaxis and this is used in the de novo CEA described below. The study by Shaker[9] does address the question regarding AI but the model is too simplistic, assuming that protection is guaranteed. Also, the population is those who have had a 'mild' reaction, which is not directly comparable with our definition of anaphylaxis, which is life-threatening. The study by Desai and Carroll 2009[8] was unfortunately too poorly reported to be useful.

Methods of cost-effectiveness analysis

Research questions

The analysis aimed to inform the following two questions:

1. What is the cost-effectiveness of referral to specialist allergy clinics for the diagnosis of anaphylaxis and for the prevention of future episodes and the reduction in morbidity and mortality from future episodes?
2. What is the cost-effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis including the cost implications of training in the use of the auto-injectors?

Population

The population of interest is all patients with anaphylaxis (irrespective of the cause) who needed emergency treatment.

However, as the title '... suspected anaphylaxis' suggests, there is a problem with diagnosis,[11] which includes the definition of anaphylaxis. For example, Stewart and Ewan[12] use the term 'severe' anaphylaxis and associate it with loss of consciousness or fainting. On this basis, they count 9 out of 55,000 emergency admissions. They then included 15 others to make 24 with 'generalized reactions involving hypotension and/or respiratory difficulty'. The rate of referral to SSs was [through the general practitioner (GP)] 4 out of 24. In a study by El-Shanawany *et al*.[13] in Wales, the 77 cases identified in 6 months implied a rate out of a population of about 500,000 of 30.8 per 100,000 people-years. This was much higher than the 6.7 in the UK previously estimated by Sheikh *et al*.[14] However, a more recent study in the UK by Gonzalez-Perez *et al*.[15] produced an estimate of 34.38. The El-Shanawany study[13] also revealed that the rate of referral to SSs was zero. Erlewyn-Lajeunesse *et al*.[11] selected cases of asthma, and urticarial and allergic reaction, as well as anaphylaxis according to physician diagnosis (in the absence of a gold standard) to test diagnostic criteria. This could imply that the suspected population is composed essentially of those suffering an allergic reaction albeit less severe as well as those with asthma. However, this Guideline definition rules this out by including: '... rapidly developing life-threatening airway, breathing and/or circulation problems ...' (http://www.nice.org.uk/nicemedia/live/12346/52120/52120.pdf, p. 1).

This fits with the definition used by Brown *et al*.[16] and, therefore, implies that, in the absence of a known trigger, other conditions that cause such life-threatening problems might be included in the population and might thus be referred to SSs. Indeed, in the absence of further information on the nature of those patients seen in a SS, an increase in referral, as is being considered, might actually increase the prevalence of patients not suffering from anaphylaxis.

However, in the latest UK guidelines for emergency treatment[17] there is a recommendation that all of those who are suffering from anaphylaxis should be referred to a SS and there is no mention of any difficulty in diagnosing anaphylaxis. Indeed, the suggestion is that the diagnosis of anaphylaxis has been made in the vast majority of cases by discharge, other possible diagnoses having been ruled out. It is on this basis that the comparison is between SSs and standard care (SC), given definite diagnosis of anaphylaxis.

Comparators

The following combinations were considered in the model:

SC, no AI: SC plus no prescription of AIs where SC is defined as the absence of referral to a SS. It is not defined any further but is expected to consist of no more than GP consultation. AIs come in the form of either EpiPen or Anapen (Lincoln Medical Ltd, Salisbury, UK) [*British National Formulary* (BNF) no. 61[18]] and in several doses, recommended as 500, 300 and 150 g for adults, children aged 6–12 years and children aged <6 years, respectively.[17] There is little variation in cost and so the cost of AI was based on the current cost of EpiPen of £26.45 (note that this value includes a price reduction that, at time of writing, had not

been reflected in BNF 61[18]). Based on expert opinion, it was assumed that AIs should be replaced every 12 months, that adults require two AIs at any one time, and that children require four (because it is common practice to keep two at school and two at home).

SC plus AI: Injectors are recommended in the latest guidelines by the Resuscitation Council UK, to be prescribed for all patients with '… life-threatening features' (p. 162).[17]

SS no AI: All patients with suspected anaphylaxis are referred to a SS in accordance with the same guidelines: 'All those who are suspected of having had an anaphylactic reaction should be referred to a specialist in allergy' (p. 158).[17] The same guideline goes on to state: 'All patients presenting with anaphylaxis should be referred to an allergy clinic to identify the cause, and thereby reduce the risk of future reactions and prepare the patient to manage future episodes themselves' (p. 166).[17]

SS plus AI: All patients both attend a SS and are prescribed AIs.

Framework

Given the lack of CEA evidence, a cost–utility analysis[19] was undertaken with costs and quality-adjusted life-years (QALYs) considered over patients' lifetimes from a UK NHS perspective in accordance with NICE methods guidance.[20] Costs were in 2011 GB pounds (£) and an annual discount rate of 3.5% was used. Despite these treatments being for short-term use, a lifetime horizon is most appropriate to capture the full impact of treatment.

Model structure

A Markov model[21] was constructed with mutually exclusive health states. The model simulated the course of events in a hypothetical cohort of persons with anaphylaxis who had been treated in an emergency care setting in the UK, aged ≥6 years. The model initially divides the cohort according to their relative incidence (referred to as 'trigger probability'), into the four main causes of anaphylaxis: drugs (including medication, biologics, vaccines and anaesthetics), insects (stings), food and idiopathic origin[11] (see *Trigger probability*). In the model, as time progresses, persons move from one state to another state according to a set of transition probabilities (see sections on model parameters below: *Rate of recurrence*, *Mortality rate*, *Idiopathic treatment* and *Venom immunotherapy*). The cycle length of the model was set to 3 months.

A cycle length of 3 months was chosen for convenience in modelling rates of recurrence as probability of a single recurrence event, as it can be shown that the longer the period the greater the error. Intuitively, this can be understood by considering that the longer the period then the greater the probability of more than one event occurring. For example, using the probability density function of the Poisson distribution, the probability of one event in 3 months with an annual rate of 0.28 (that of idiopathic cause, which is the highest of all causes used in the model) is 0.065. Although actually more than one event could occur in this time, the probability of two events is only 0.002 and that of more events is extremely small at only about 0.00005. Given the large amount of uncertainty in all parameter estimates, it was believed to be acceptably close and all other rates (for food, drug and insect causes) are no larger than about 0.12, which produces even less of an error. A shorter cycle length could have been used but there would still have been an error, although smaller, and this would have only increased model calculation time.

The health states are 'death', 'at risk' (of recurrence), 'recurrence' and, for idiopathic cause only, 'remission' (*Figure 2*). All members of the cohort begin in the 'at-risk' state and move in the next 3 months to the 'recurrence' state, with a probability according to the rate of recurrence (see explanation above), except if the cause was not known (i.e. idiopathic cause), where recurrence could occur only if remission had not.

Those in the 'at-risk' or 'remission' states (idiopathic and insect only) were assumed to have general population age and sex-specific mortality.[22] Those in the 'recurrence' state had this mortality plus an additional probability. First, they were divided into those who used an AI or not, according to a probability

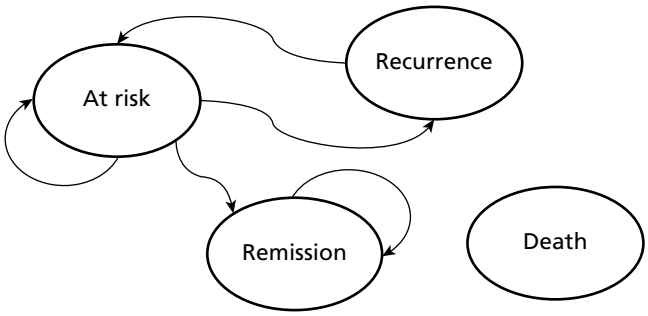

FIGURE 2 Diagram showing the health states and transitions between them; transitions can occur from any live state to the death state.

for correct use (see *Mortality*). For both SS and SC plus AI, this probability was greater than zero, as all patients were assumed to be prescribed two injectors, each of which has a 6-month life. It was then assumed that all would continue be supplied and thus incur the cost until death, unless there was remission. In the 'no AI comparators' the probability was zero.

Under SC, unless there was remission (idiopathic and insect only), the recurrence rate was assumed to be constant. This was based on a lack of evidence to the contrary presented in any of the guidelines or the systematic review. The effectiveness of SSs, therefore, was partly mediated by a change in recurrence rate, which depends on trigger and is explained below.

Food and drug

Based on the various guidelines and expert opinion it was assumed that the effect of SSs on recurrence was mediated by the identification and then advice to avoid the trigger, which then reduced the rate of recurrence.

Idiopathic

The possibility of remission for idiopathic was based on two international guidelines,[23,24] in which it is suggested that it will occur spontaneously, although those patients classed as having 'frequent' recurrences (more than two in 2 months or more than six in 1 year) are recommended to be prescribed prednisolone. It was therefore assumed that the effect of SSs on recurrence was mediated by treatment (with prednisolone) of those suffering from frequent episodes of recurrence (see *Idiopathic treatment*). This implies an advantage of SSs over SC, as with SSs remission can occur in both the frequent and the infrequent, whereas with SC remission was assumed to occur only in the infrequent.

Insect

It was assumed that effect of SSs on recurrence was mediated by remission due to identification and then treatment with venom immunotherapy (VIT) in accordance with an international guideline,[25] guided by expert opinion as to regime (see *Venom immunotherapy*). This involved a total period of treatment of about 3 months with an initial 'build-up' phase of about 10 weeks. Not everyone is offered this treatment: some refuse and some drop out. Therefore, the recurrence rate is a function of probability of uptake, dropout and effectiveness.

The effect of SSs was also mediated through greater compliance (correct use) of AIs on the basis that training should be better, and thus reduced mortality.

Finally, the effect of both SSs and AI also included an increase in utility in the 'at-risk' state in order, in accordance with expert opinion, to capture the general improvement in well-being.

Parameterisation

All parameter values were estimated using the best evidence available and according to best practice.[20,26] Unfortunately, the systematic review revealed only few and generally poor-quality studies on rates of recurrence by trigger and none comparing the effectiveness of SSs versus SC or the effectiveness of AIs (by any measure, e.g. reduction in rate of recurrence), which is confirmed by other recent reviews.[17,27–29] All other parameter estimates were chosen in order to be as UK relevant as possible, based on evidence that was either directly cited by recent UK or international guidelines or found by citation searching from these sources. This method was chosen in order to maximise the efficiency of obtaining high-quality relevant estimates.

In accordance with best practice and the principle that expert opinion proxies for the beliefs of the decision-maker, which, in effect, is NICE, expert opinion from the GDG was sought for all parameters. This was done either to provide an estimate in the absence of evidence or to provide an estimate based where possible on the presentation of some evidence. Practically, it involved asking during a GDG meeting for consensus as to the 'most likely', 'lowest' and 'highest' values of parameters. In order to facilitate this, where possible data from the literature were presented and in these cases, the source is given as 'expert opinion and based on [data]'.

Because the latest NICE guidance[20] demands probabilistic sensitivity analysis (PSA),[30] parameters to estimate distributions were also estimated. Where the source was deemed to be good enough the sampling distributions of the probabilities (beta for binomial and Dirichlet for multinomial) were used.[31] In most other cases, a triangular distribution was used, based on expert opinion elicited as the lowest, most likely and highest values. In order to make the expected value the same as the most likely, all triangular distributions were symmetrical. The table containing the estimates and summarising the sources is split into several tables between sections in order to facilitate explanation, although it is also presented in full in *Appendix 5*.

Population characteristics

For the population in the model the following two (*Table 6*, parameters 1–2) assumptions have been made: 50% of the patients in the model are male and the starting age is 30 years. Although there is a little variation between studies as to what age defines someone as a child, we assume that it is <17 years.

Rate of recurrence

For the model, the annual rate of recurrence of anaphylaxis caused by drugs after referral to SSs was based on expert opinions (*Table 7*, parameter 3). This rate will probably be very low based on the idea that it is very unlikely that the same drugs which caused the first anaphylactic reaction will be prescribed for the same patient again.

Parameter 4, the annual rate of recurrence of anaphylaxis due to food in SSs, was based on the data of two longitudinal prospective observational studies on the effectiveness of a management programme providing advice on nut avoidance and emergency medication in the UK. These two studies reported only three recurrences out of over 13,000 observation months, which is equivalent to a rate of about 0.003 per patient-year in adults and/or children who were diagnosed for peanut or tree nut.[33,34] However, these studies were not controlled trials. Furthermore, nut allergy patients are only a subgroup of all anaphylactic patients who will be referred after emergency treatment to specialist allergy care. Therefore, based on expert opinion, a more conservative estimate of 0.01 was chosen, although the minimum of 0 allowed for the possibility of very effective treatment.

Under SC, the most likely values for the annual rate of recurrence of anaphylaxis due to food or drugs and idiopathic (see *Table 7*, parameters 5 and 6) in current practice were based on the findings of a prospective study of 432 patients who were referred to a community-based specialist practice in Australia.[7] This was the only study from the systematic review that reported rates of recurrence by cause and the results had to be read off a graph (figure 1, p. 1037). The rate of anaphylaxis due to food was calculated by a

TABLE 6 Population characteristics

No.	Parameter	Name parameter in model	Distribution type	Base case	Sources
1	Cohort start age	startage	N/A	30	Assumption
2	Proportion of cohort male	pmale	N/A	0.5	HES 2010[32] (see *General model assumptions*)

HES, Hospital Episode Statistics; N/A, not applicable.

TABLE 7 Rates of recurrence

No.	Parameter	Name parameter in model	Distribution type	Minimum	Most likely	Maximum	Sources
3	Annual rate of recurrence of anaphylaxis due to drugs with SSs	dprecurdrugSS	Triangular	0	0.001	0.002	Expert opinion
4	Annual rate of recurrence of anaphylaxis due to food with SSs	dprecurfoodSS	Triangular	0	0.01	0.02	Expert opinion and based on Ewan *et al*. 2001,[33] p. 753, text Paragraph heading: 'Severity of follow-up reaction' No one with a severe initial reaction ($n = 49$) had a further severe reaction Ewan *et al*. 2005[34] Table 1, p. 112: Severe follow-up reaction grade 5 $r = 3$ (0.5%), $n = 567$ (100%)
5	Annual rate of recurrence of anaphylaxis due to food with SC	drecurfood	Triangular	0.05	0.11	0.16	Expert opinion and based on Mullins 2003,[7] figure 1, p. 1037
6	Annual rate of recurrence of idiopathic anaphylaxis with SC	drecuridio	Triangular	0.05	0.28	0.51	Expert opinion and based on Mullins 2003,[7] figure 1, p. 1037
7	Annual rate of recurrence of anaphylaxis due to drugs with SC	drecurdrug	Triangular	0.05	0.12	0.19	Expert opinion and based on Mullins 2003,[7] figure 1, p. 1037
8	Annual rate of recurrence of anaphylaxis due to insect sting with SC	drecurinsect	Triangular	0.05	0.10	0.15	Expert opinion and based on Gonzalez-Perez 2010,[15] pp. 1101–2 Last paragraph, p. 1101: 'Anaphylaxis is associated with high risk of recurrence but is highly unpredictable. Estimated rate: 0.06 to 0.11 episodes per year'

combination of figures on incidence of anaphylaxis due to food and exercise-induced anaphylaxis (as these were not separated in the report) (*Table 8*).

The average across all foods was calculated by dividing the total annual number (sum across all *r* per year in the table) by the total number at risk (summing across all *n* in the table). The annual rate of recurrence of anaphylaxis due to insect sting (see *Table 7*, parameter 8) was based on the findings of the most recent (2010; 343 with anaphylaxis) UK study (Gonzalez-Perez *et al*.[15]), as figures for the Australian population are not likely to resemble those for the UK population because the risk of experiencing an insect bite or sting is much higher in Australia than in the UK. Gonzalez-Perez *et al*.[15] reported a range from about 0.05 to 0.1 for any cause and so, given expert opinion, the higher rate was chosen as the most likely.

Based on expert opinion, 0.05 was chosen as the lowest value for all causes and the highest value followed from making the distributions symmetrical.

Trigger probability

As stated in literature, it is difficult to calculate the exact incidence rates of anaphylaxis as a result of difficulties with coding, diagnosis and reporting (Sampson *et al.*[35]) and actual rates remain unclear.

In the model, the figures for probability of anaphylaxis due to insect sting and idiopathic anaphylaxis (*Table 9*, parameters 9 and 10) were estimated based on a 1-year study analysing The Health Improvement Network (THIN) database on 2.3 million patients (age 10–79 years) who had been enrolled with a GP in the UK for at least 1 year (Gonzalez-Perez *et al*.[15]).

In the model, the probabilities that anaphylaxis was due to drug were specified for adults and children (see *Table 9*, parameter 11) using the figures of a retrospective study on emergency calls for allergic reactions within greater Manchester, also in a 1-year period, by the North West Ambulance Service in the UK (Capps *et al*.[36]).

As can be seen, all probabilities were converted from multi- to binomial (essentially from marginal to conditional), which produces exactly the same result as if they had been treated as multinomial. This was done for ease of use in the model software (TreeAge Software, Inc., Williamstown, MA, USA, 2009). This means that the probability of idiopathic anaphylaxis is calculated first from *r*/*n* (103/343). Then, the probability of insect given not idiopathic is calculated given that idiopathic is ruled out from 46/240.

TABLE 8 Rates of anaphylaxis per year for food and number at risk in the sample

Food	Rate (no. of episodes per person at risk per year)	No. of persons at risk (*n*)	No. of episodes per year (*r*)[a]
Meat	0	7	0
Soy	12	8	96
Cow's milk	11	19	209
Crustaceans	7	27	189
Fish	3	22	66
Wheat plus exercise	40	29	1160
Fruit/vegetables plus exercise	15	48	720
Egg	10	49	490
Nuts	9	112	1008

a Number of episodes per year (*r*), calculated by multiplying the rate by the number at risk (*n*).

Next, the probability of drug given being not idiopathic or insect is calculated from 19/87 or 236/303, depending on whether child or adult. The probability of food given being not idiopathic or insect or drug is then simply 1 – probability of drug.

Table 9 gives a description of the model inputs, which imply the following marginal probabilities (*r*/all anaphylaxis = *r*/343): idiopathic 30.03%; insect 13.41%; food 44.21% (children) and 12.51% (adults); and drug 12.35% (children) and 44.05% (adults).

Mortality

Details of mortality from anaphylaxis are shown in *Table 10*.

The number of deaths due to anaphylaxis in the UK was estimated from the findings reported by the working group of the Resuscitation Council (Soar *et al*.[17]). This was based partly on a set of studies using a register of deaths due to anaphylaxis compiled by Pumphrey,[37] Pumphrey and Gowland,[38] and Pumphrey and Roberts.[39] The number of anaphylaxis cases was estimated by figures for the period of 2009–10 from the Department of Health Hospital Episode Statistics (HES)[32] (www.hesonline.nhs.uk). As already stated in the section on incidence rates, both of the reported figures are likely to be underestimates, as it is difficult to diagnose and correctly code anaphylaxis, so the mortality rate will probably not vary much from this. These figures imply an annual probability of dying of 20/3517 = 0.005687, i.e. about 0.5%.

TABLE 9 Probabilities of trigger subgroups

No.	Parameter	Name of parameter in model	Distribution type	*n*	*r*	Sources
9	Probability that anaphylaxis idiopathic	didio	Beta[a]	343	103	Gonzalez-Perez 2010,[15] table V, p. 1104 = 30%
10	Probability that trigger was insect, given not idiopathic	dinsect	Beta[a]	240	46	Gonzalez-Perez 2010,[15] table V, p. 1104 = 13.41%
11	Probability that trigger was drug, given not idiopathic and not insect in child	ddrugchild	Beta[a]	87	19	Capps *et al*. 2010,[36] table 1, p. 655 = 12.4%
12	Probability that trigger was drug, given not idiopathic and not insect in adult	ddrugadult	Beta[a]	303	236	Capps *et al*. 2010,[36] table 1, p. 655 = 44.1%
	Probability that trigger was food, given not idiopathic, not insect nor drug in child	–	–	–	–	= 44.2%
	Probability that trigger was food, given not idiopathic, not insect nor drug in adult	–	–	–	–	= 12.5%

a Beta distribution: (*n*) is number at risk/sample size, (*r*) is number who had the event.

TABLE 10 Mortality from anaphylaxis

No.	Parameter	Name of parameter in model	Distribution type	*n*	*r*	Sources
13	Annual probability of dying given anaphylaxis and presence of emergency services and current AI use	ddieanaph	Beta	3517	20	Soar *et al.* 2008[17] HES 2010[32]

Effect of adrenaline injectors on mortality

In order to estimate the effect of the AIs, it is necessary to 'subtract' out the effect of the injectors in order to estimate the probability of death with no AI. Put another way, the estimate of mortality shown above is lower than the mortality rate due to anaphylaxis in the presence of both the use of emergency services (referred to as 'ambulance') and AIs. Therefore, to estimate the effect of AI, we first need to estimate an 'underlying' rate plus ambulance effect only. Note that all of the calculations to estimate the probability of dying given no AI were performed in TreeAge from the parameters for death given emergency services and current AI use and parameters for time to death and ambulance response times shown below (*Table 11*).

Having calculated the probability with no AI, the effect of AIs can be applied, either with SC or with SSs. As will be explained below, the parameter in the model that estimates the effect of SC or SSs is the proportion of correct use, which would be expected to be higher with SSs than with SC.

In the absence of direct evidence as to how many deaths have actually been prevented by AIs, there are several steps in the calculation, which implies the need to use several parameters and, thus, the need to make some assumptions. However, it will be attempted to make these explicit and justified where possible. Also, as with all parameters, they were all subject to sensitivity analysis. Before the exposition, in order to improve clarity, the result of the calculations is first summarised by intervention (presence of AIs or ambulance service) in *Table 11*.

First, it was assumed that the effect of ambulance or AI depended on the time between exposure to trigger and death. Of course, with idiopathic this would be impossible, as there is no trigger. Indeed, the register by Pumphrey,[37] and summarised by Soar *et al.*,[17] does contain these data for food, drug [oral and injected (although only 'oral' used, as 'injected' most likely to be administered in a health-care setting)] and insect. However, the total number of observations (111) is small. Therefore, time to death was estimated, making the assumption that the average across these three groups would apply to any cause including idiopathic. In practice, all of these times were times to first cardiac arrest, but, given that all individuals died, it is assumed that, in order to prevent death, adrenaline must be administered before this point. It was also assumed that the time to death observed in those who died was similar to that in those avoided by either the emergency services (referred to as 'ambulance') or AI.

Therefore, first, the proportions dying in each of the categories reported by Soar *et al.*[17] (2.1–4.5, 4.6–9.9, 10–20 and >20 minutes) was estimated, as shown in *Table 12*.

'Drug' only included oral and not injected, on the basis that injected would have been administered by a health-care professional with little need for AI. These values, which were inputs in the model, imply the following proportions in each of the time categories shown in *Table 13*.

Using the probabilities of each trigger (excluding idiopathic) from the same sources as used above allows calculation of the probabilities of time to death for any trigger.

For example, about 62% of cases of patients with anaphylaxis from any cause would still be alive for up to 20 minutes, which means that death might be prevented by the arrival of an ambulance within that time. Therefore, to calculate the deaths that could be prevented by AI, one needs to first estimate the effect of the ambulance service. For example, if 100% of response times were <4.5 minutes then there would be no need for AI but also there would be no deaths, which, of course, is not the case.

Therefore, to estimate the response times, the data from an audit of ambulance services were used;[40] the proportions of responses in each of the reported categories (<8, 8–18 and >18 minutes) were estimated for each of the emergency categories, A (essentially life-threatening) and B, shown in *Table 14*.

The category '<8 minutes' is not reported for 'B' and so it was assumed to be zero. This is unlikely to be a problem, as the proportion of calls to anaphylaxis in category B is likely to be very small. Indeed

TABLE 11 Mortality by intervention (all figures are calculated except the 20 deaths given current practice)

Intervention	Percentage of anaphylaxis cases that result in death	Relative risk of death (vs no intervention)	No. of deaths per year (from 3517 cases of anaphylaxis)
No intervention	6.473	1	228
Ambulance only	0.838	0.129	29
Ambulance plus AI (current practice[a])	0.569	0.096	20
Ambulance plus perfect use[b] of AI	0.025	0.004	1

a Current practice is equivalent to SC, i.e. about 44% correct use of injector across all ages (see text).
b Perfect means 100% correct use, but note that risk is not zero because no deaths saved under 4.6 minutes (see text).

TABLE 12 Model parameters of time to die for each trigger of anaphylaxis

No.	Parameter	Name of parameter in model	Distribution type	*r* in categories (2.1–4.5, 4.6–9.9, 10–20 and >20 minutes)	Sources
14	Time to die, food	dtimediefood	Dirichlet	(0; 0; 9; 50)	Soar *et al.* 2008[17]
15	Time to die, drug	dtimediedrug	Dirichlet	(0; 2; 4; 7)	Soar *et al.* 2008[17]
16	Time to die, insect	dtimedieinsect	Dirichlet	(2; 4; 20; 13)	Soar *et al.* 2008[17]

TABLE 13 Distribution of time to death by trigger of anaphylaxis

	Categories (minutes)			
Trigger	2.1–4.5	4.6–9.9	10–20	>20
Food	0	0	0.152542	0.847458
Drug (oral)	0	0.153846	0.307692	0.538462
Sting	0.051282	0.051282	0.512821	0.384615
Any trigger	0.003889	0.096853	0.273614	0.625645

TABLE 14 Model parameters of ambulance response times

No.	Parameter	Name of parameter in model	Distribution type	*r* in categories (<8, 8–18 and >18 minutes) or *n*	*r*	Sources
17	Ambulance response time, category A	DtimeA	Dirichlet	(1, 442, 519; 437, 973; 60, 160)	N/A	NHS Information Centre 2010[40]
18	Ambulance response time, category B	Dtime19B	Beta	2, 559, 126	2, 322, 793	NHS Information Centre 2010[40]

N/A, not applicable.

the figures used were from Capps *et al.*,[36] where there were <10% in 'B' (referred to as 'amber' in that study). 'Purple' and 'red' were assumed to be equivalent to 'A'. The category '<8 minutes' was assumed to correspond to 4.6–9.9 minutes, assuming that response time would never be <4.6 minutes. The categories '8–18 minutes', '10–20 minutes', '>20 minutes' and '>18 minutes' were assumed to be equivalent. These *r* and *n* values, used as inputs in the model, imply the proportions shown in *Table 15*.

The proportions for any category are calculated by taking the average, weighted by the total numbers in each of the categories.

This, therefore, permitted the estimation of the proportion of all deaths that would not be saved by ambulance and thus could be saved only by correct and timely use of AI. For example, all of those with a time to death of <4.6 minutes would not be prevented, whereas the proportion who would still die in the '10–20 minutes' category would be only those for whom the ambulance response time was in the >18-minute category. The formula is:

$$\begin{aligned}\text{Propnot}_{amb} = {} & \text{Propnot}_{amb}\{2.1\text{–}4.5 \text{ minutes}\} \\ & + \text{Propnot}_{amb}\{4.6\text{–}9.9 \text{ minutes}\} \\ & + \text{Propnot}_{amb}\{10\text{–}20 \text{ minutes}\} \\ & + \text{Propnot}_{amb}\{>20 \text{ minutes}\}\end{aligned} \quad (1)$$

where Propnot_{amb} is the proportion of deaths that would occur as a result of anaphylaxis, which are *not* prevented by ambulance, which depends on the response time distribution so that:

$$\begin{aligned}\text{Propnot}_{amb} = {} & \text{Propdie}\{2.1\text{–}4.5 \text{ minutes}\} \\ & + ((1 - (\text{Propresp}\{<8 \text{ minutes}\} \times 0.5)) \times \text{Propdie}\{4.6\text{–}9.9 \text{ minutes}\}) \\ & + ((1 - \text{Propresp}\{<8 \text{ minutes}\} - (\text{Propresp}\{8\text{–}18 \text{ minutes}\} \times 0.5)) \times \text{Propdie} \\ & \{10\text{–}20 \text{ minutes}\}) \\ & + ((1 - \text{Propresp}\{<8 \text{ minutes}\} - \text{Propresp}\{8\text{–}18 \text{ minutes}\} - (\text{Propresp} \\ & \{>18\} \times 0.5 \text{ minutes})) \times \text{Propdie}\{>20 \text{ minutes}\})\end{aligned} \quad (2)$$

where Propdie is the proportion who die in each time period, shown in *Table 13*, and Propresp is the proportion who respond within that time period, shown in *Table 15*. It can be seen that Propnot (2.1–4.5 minutes) = Propdie (2.1–4.5 minutes), because it is assumed that the ambulance never arrives that early. It can also be seen that a factor of 0.5 is used for some proportions; these are where the response time period is the same as the time period for death. Multiplying by 0.5 implies that only 50% of response times are less than time to die. This is an assumption given the lack of more precise data within each period.

TABLE 15 Distribution of ambulance response times

	Categories (minutes)		
Ambulance	<8	8–18	>18
Category A	0.743316	0.171142	0.085542
Category B	0	0.907651	0.092349
Any category	0.672829	0.240983	0.086187

From the data in the tables:

$$\begin{aligned}\text{Propnot}_{amb} &= 0.003889 \\ &+ ((1-(0.672829 \times 0.5)) \times 0.096853) \\ &+ ((1-0.672829-(0.290353 \times 0.5)) \times 0.273614) \\ &+ ((1-0.672829-0.290353-(0.036818 \times 0.5)) \times 0.625645) \\ &= 0.129472 \end{aligned} \quad (3)$$

This means that about 13% of anaphylaxis deaths are not prevented by ambulance.

Now to calculate the effect of AIs it was assumed that all AIs, if used successfully, would be used within the '4.6–9.9 minutes' category. This implies that all of those deaths not prevented by ambulance in <4.6 minutes would still not be prevented. However, this does not imply that all deaths in the time window of 4.6 minutes or longer would be prevented, as this applies to only those who actually use the injector correctly; there is another parameter, which is the proportion who do this, which might be <100%. Indeed, in the Capps *et al.* study,[36] only about 44% (53/119) of those who eventually were given adrenaline (by ambulance or injector) received an adrenaline by AI. This means that the proportion of deaths not saved by either ambulance or AI can be estimated:

$$\begin{aligned}\text{Propnot}_{amb+AI} &= \text{Propnot}_{amb}\ \{2.1–4.5\} \\ &+ (\text{Propnot}_{amb}\ \{4.6–9.9\} \times \text{Pcorrect} \times 0.5) \\ &+ (\text{Propnot}_{amb}\ \{10–20\} \times \text{Pcorrect}) \\ &+ (\text{Propnot}\ \{>20\} \times \text{Pcorrect}) \end{aligned} \quad (4)$$

i.e. the proportion of deaths prevented by AI in each time period is the probability of correct use, Pcorrect (53/119) multiplied by the proportion that would not have been prevented by ambulance with a correction factor of 0.5 for the period 4.6–9.9 minutes only. Therefore, it can be calculated that:

$$\text{Propnot}_{amb+AI} = 0.087852 \quad (5)$$

i.e. about 9% of deaths are prevented by both ambulance and AI use. This is therefore the proportion of deaths from anaphylaxis (without any intervention) that would remain in the event of current ambulance service provision and current AI use. Therefore, to calculate the overall (no intervention) mortality rate, Pdeath, use:

$$\text{Pdeath} = \text{Nno intervention}/\text{Nanaphylaxis} \quad (6)$$

$$\text{Nintervention} = \text{Pintervention} \times \text{Nno intervention} \quad (7)$$

where 'Nintervention' is the number of deaths with current service and AI use, which is 20 (see *Table 10*); 'Pintervention' is the proportion of deaths not saved, which was calculated to be 0.087852; and 'Nno intervention' is the number of deaths that would have occurred and 'Nanaphylaxis' is the number of cases of anaphylaxis, which is 3517 (see above).

Substituting (7) into (6) gives:

$$\begin{aligned}\text{Pdeath} &= \text{Nintervention}/\text{Propnot}_{amb+AI}/\text{Nanaphylaxis} \\ &= 20/0.087852/3517 \\ &= 0.064729 \end{aligned} \quad (8)$$

i.e. the probability of dying from anaphylaxis without any treatment would be about 6%, which would result in $3517 \times 0.064729 =$ about 228 deaths per year.

Therefore, we can now fulfil the aim of this section and calculate the probability of dying with ambulance and no AI, which is:

$$\begin{aligned} \text{PdeathnoAI} &= \text{Propnot}_{amb} \times \text{Pdeath} \\ &= 0.129472 \times 0.064729 \\ &= 0.008381, \text{ which would result in } 3517 \times 0.008381 = \text{about 29 deaths per year} \end{aligned} \quad (9)$$

'PdeathnoAI' is the probability of death used in the model for no injector use. This means that 'Pdeath AI' is the probability of death with correct AI use (recall that those deaths at <4.6 minutes would not be prevented even with correct use), which can be calculated by assuming that the proportion given AI is 100%:

$$\begin{aligned} \text{PdeathAI100\%} &= 0.00389 \times 0.064729 \\ &= 0.000252, \text{ which would result in } 3517 \times 0.000252 = \text{about one death per year} \end{aligned} \quad (10)$$

This is because the only deaths not prevented by 100% correct AI use are those that occur within 4.5 minutes. This means that, whereas current AI use (44%) saves about nine deaths per year, if AI use was 100% correct, there would be only about one death per year, saving an extra eight lives per year.

In the model, 'Pdeath' is calculated by using 'Pcorrect' from Capps *et al.*,[36] 53/116 (about 44%) (*Table 16*).

This is not the value used to estimate the probability of correct use in the model, i.e. during the cohort simulation, as Capps *et al.*[36] also presented separate values for children (<15 years) and adults (shown with the value for SS in *Table 17*).

TABLE 16 Model parameter for current probability of correct use of AI used only to calculate underlying probability of death due to anaphylaxis, 'Pdeath' (see text)

No.	Parameter	Name of parameter in model	Distribution type	*n*	*r*	Sources
19	Probability of correct use of AI with SC	dpinjector	Beta	116	53	Capps *et al.* 2010[36] *n* = table 3, p. 655 at any time *r* = before ambulance arrived

TABLE 17 Model parameters for probability of correct use of AI with SC

No.	Parameter	Name parameter in model	Distribution type	*n*	*r*	Sources
20	Probability use injector correctly with SC in child	dinjectorchild	Beta	15	10	Capps *et al.* 2010[36] *n* = table 3, p. 655 at any time *r* = before ambulance arrived (child)
21	Probability use injector correctly with SC in adult	dinjectoradult	Beta	101	43	Capps *et al.* 2010[36] *n* = table 3, p. 655 *r* = before ambulance arrived (adult)

The probability of using an AI given SC (see *Table 17*, parameters 20 and 21) was based on the figures of use of AIs before arrival of the North West Ambulance Service (Capps *et al.*[36]) and the total number of patients who received adrenaline. These figures are much lower than the 514 patients (adults and children) who eventually presented with symptoms that might be consistent with anaphylaxis, i.e. this implies that not all patients who had the symptoms of an anaphylactic reaction needed/received an adrenaline injection for treatment.

It is expected that the compliance of patients who received education (in SSs) will increase (*Table 18*, parameter 22). Compliance with AIs is mainly dependent on the knowledge of how to use it in a correct way, as well as the will to ensure that it is easily accessible and to use it when necessary. However, no estimate could be found of the effect of SS on compliance. Therefore, in the base case, 90% correct use was assumed, although recall that this means that those with a very short time to die ('<4.6 minutes' category from Soar *et al.*[17]) will still die (see *Table 18*). This makes the estimate more conservative.

Idiopathic treatment

Estimates to calculate probability of remission came from an observational study by Krasnick *et al.*,[10] which was used because it was the only study that could be found that included any time to event data to enable the probability of remission to be estimated. Data on years of follow-up and years in remission were provided, from which time to remission could be calculated by subtraction. *Table 19* shows the data extracted for frequent and infrequent recurrence categories.

Only those and all of those experiencing frequent episodes received treatment with prednisolone. As this implies specialist provision, the probability of remission with SSs is the sum of that with frequent episodes (plus treatment) and infrequent episodes (no treatment), whereas the probability of remission with SC is only that of the infrequent episodes.

Because data on rate of recurrence were not available separately for those experiencing frequent or infrequent episodes, it was assumed that the same (average) rate (see parameter 6, *Table 7*) applied to both. Thus, when remission occurs, the average rate would decrease, as for those in remission the rate is zero. Therefore, the advantage of SSs over SC can be explained in the following way. The probability of recurrence given SSs is the sum across both the frequent, some of whom go into remission due to treatment, and the infrequent, some of whom go into remission spontaneously. However, the probability of recurrence given SC is the sum across the frequent, *none* of whom go into remission, and the infrequent, some of whom go into remission spontaneously.

From the data in *Table 19* the median of time to remission was calculated, which was then used to inform the probability of remission (per cycle length, i.e. 6 months) in the model where, according to the definition of the median, the probability of remission per cycle (median time) = 0.5 and a constant rate (exponential model) assumed. The median was estimated by assuming that censoring (no remission at follow-up) indicated remission. This is a conservative estimate of time to remission. However, excluding the censored data produced a lower estimate and so the estimates of 4 and 1.5 for frequent are probably not too low. These estimates were used to form the most likely with assumptions as to the low and high (*Table 20*).

TABLE 18 Model parameters for probability of correct use of AI with SS

No.	Parameter	Name parameter in model	Distribution type	Minimum	Most likely	Maximum	Sources
22	Probability use injector correctly with SSs	dpinjectorSS	Triangular	0.8	0.9	1	Assumption

TABLE 19 Data (years of follow-up and years in remission) extracted from Krasnick *et al.*,[10] used to calculate time to remission

Recurrence					
Frequent			Infrequent		
Years of follow-up	Years in remission	Time to remission	Year of follow-up	Years in remission	Time to remission
7	4	3	6	2	4
8	2	6	5	5	0
8	4	4	3	2	1
8	8	0	6	4	2
12	11	1	5	4	1
7	6	1	6	5	1
10	2	8	6	6	0
6	2	4	5	4	1
5	3	2	12	9	3
9	9	0	10	3	7
6	N/R	6	6	0	6
18	N/R	18	9	1	8
7	N/R	7	6	N/R	6
9	N/R	9			
5	N/R	5			

N/R, not reported.

TABLE 20 Parameters to estimate probability of remission

No.	Parameter	Name of parameter in model	Distribution type	Low	Most likely	High	Sources
23	Median time to remission in frequent idiopathic	dmedianfreq	Triangular	2	4	6	Based on data from Krasnick *et al.* 1996[10]
24	Median time to remission in infrequent idiopathic	dmedianinfreq	Triangular	1	1.5	2	Based on data from Krasnick *et al.* 1996[10]

It was assumed that the rate of recurrence among those who did not go into remission would remain the same, which is probably an underestimate as the median time to remission is longer in those with frequent recurrence. Remission is still allowed to occur with SC, although only in those with infrequent recurrence, but also with no rise in the remaining rate so that there should be little bias towards either SC or SSs.

The proportion of frequent anaphylaxis (0.5) was also taken from the study by Krasnick *et al.*,[10] which uses the same definition of frequent as the guideline, shown in *Table 21*.

TABLE 21 Proportion of idiopathic patients who have frequent recurrence

No.	Parameter	Name of parameter in model	Distribution type	*n*	*r*	Sources
25	Proportion of idiopathic that are frequent	dfreqidio	Beta	56	28	Krasnick *et al.* 1996[10]

Venom immunotherapy

Venom immunotherapy is indicated for patients who have a history of severe systemic reaction to a sting.[41] The effectiveness of VIT (*Table 22*, parameter 26) is estimated to be 85%; this is based on several studies that report a range of effectiveness of 75–95% (Krishna and Huissoon).[42] There is also a potential risk of anaphylaxis with VIT and, thus, increased cost and reduced utility but these are assumed to be negligible, especially given that the therapy is administered in a clinic where there is access to adrenaline and other emergency care (based on Cox 2011).[25] As VIT is time-consuming in terms of both frequency of treatments and total duration of therapy, and there is also the possibility of adverse reactions caused by VIT, we presume that not all patients will continue immunotherapy for 3 years (parameter 27, see *Table 22*). This figure is based on the finding of Goldberg *et al.*,[43] who reported a dropout rate of 40% in a study evaluating the attitudes of patients in Israel with insect venom allergy regarding after-sting behaviour and proper administration of adrenaline. We assumed that in the UK, 10 years later, the dropout rate of VIT would be much lower (about 20%) as a result of better care and fewer adverse events. Also, because of knowledge of these problems and the fact that, depending on the results of skin and anti-immunoglobulin E (IgE) testing, not everyone is eligible (as low as 65% according to Cox *et al.*)[25] it was conservatively estimated that uptake would be about 60% (parameter 28; see *Table 22*).

Health valuation estimation

For the calculation of QALYs of the NICE reference case[20] we needed an estimate of utility values (usually between 0 and 1), ideally obtained using the EuroQoL (EQ-5D index) instrument.

Utility (with no adjustment for anaphylaxis) was estimated as a function of age from a large recent EQ-5D US population study.[44] Decrements were then applied to each state except for that of 'remission'.

For the estimation of the utility decrement due to being at risk of recurrence of anaphylaxis, the study by Voordouw *et al.*[45] was used. This case–control study[45] using a postal survey was designed to evaluate the household costs associated with food allergy and also reported EQ-5D index data of 125 patients. The utility decrement was estimated as 0.08 (based on the difference between the values reported of 0.887 for cases and 0.803 for control subjects; $p < 0.05$) (*Table 23*, parameter 29).

We presumed that the impact of anaphylaxis will be very short but profound. The estimation of mean duration of having recurrence of anaphylaxis (parameter 30; see *Table 23*) was based on the finding that the mean loss of about 9 whole quality-adjusted life-days for severe allergic reaction due to penicillin is equivalent to utility decrement of the whole of the age-dependent utility for 1–9 days, reported in another CEA.[46] Unfortunately, this value was no obtained using the EQ-5D instrument, but appeared to be based on an assumption. Indeed, the mean length of hospital stay reported in the HES[32] is only about 1 day, but this is likely to be an underestimate of the duration of the effect on well-being of recurrence. Therefore, a value half-way between these extremes was chosen, which is the expected value of a uniform distribution bounded by 1 and 9.

Finally, there was expert opinion that the reassurance provided by attending an SS through, for example, diagnosis of trigger and learning how to avoid triggers, as well as the provision of AI, should reduce the utility decrement due to the condition (parameter 31; see *Table 23*). Therefore, in the absence of any evidence as to the extent of this effect, ranges of 0–0.5 for a factor to be multiplied by a utility increment equal to the decrement due to anaphylaxis, were chosen for each of SSs and AI (parameter 32; see

TABLE 22 Venom immunotherapy parameters

No.	Parameter	Name of parameter in model	Distribution type	Base case	Range		Sources
					Minimum	Maximum	
26	Effectiveness of VIT	dpeffectVIT	Triangular	0.75	0.85	0.95	Expert opinion and based on Krishna 2011[42]
27	Dropout	dropout	Triangular	0.1	0.2	0.3	Expert opinion and based on Goldberg[43]
28	Uptake of VIT	duptakeVIT	Triangular	0.4	0.6	0.8	Expert opinion and based on Cox *et al.* 2011[25]

TABLE 23 Utilities

No.	Parameter	Name of parameter in model	Distribution type	Low	Most likely	High	Sources
29	Utility decrement due to at risk	duatrisk	Triangular	0.00	0.08	0.1	Expert opinion and based on Voordouw 2010[45]
30	Duration of recurrence	ddurationrecur	Uniform	1	N/A	9	Expert opinion and based on Neuner *et al.* 2003[46]
31	Utility factor with SSs	duSSimprove	Triangular	0	0.25	0.5	Assumption based on expert opinion
32	Utility factor with AI	duAIimprove	Triangular	0	0.25	0.5	Assumption based on expert opinion

N/A, not applicable.

Table 23). This means that, at best (factor = 0.5 for SS + 0.5 for AI = 1), the combination could completely remove the decrement and, at worst, have no effect (factor = 0).

Resource use and unit cost estimation

Table 24 gives a description of the unit costs (in £) and the resource-use data used in the model.

The mean cost and standard error of inpatient care was estimated from the individual Primary Care Trust data for the period of 2009–10 from the Department of Health Hospital Episode Statistics (www.hesonline.nhs.uk)[32] (see *Table 24*, parameter 33).

The average costs of AIs were based on the costs reported in the BNF 61[18] (parameter 34). The lifespan of an AI was assumed to be 6 months and two prescribed or replaced at a time, based on expert opinion. Only those who were prescribed an AI incurred that cost and this was assumed to be for the rest of their lives. The costs of treatment of patients in SS were based on the NHS reference costs.[47] All individuals with anaphylaxis, regardless of trigger, incurred the cost of two appointments (one initial and one follow-up) in the first 3-month cycle of the model. These were based on the 'multiprofessional' categories: for children, Paediatric Clinical Immunology and Allergy (Service code 255) and, for adults, Clinical Immunology and Allergy (Service code 316) (see *Table 24*, parameter 35). Expert opinion was to include the cost of training in the use of the auto-injectors, i.e. there was no additional training cost.

Only those with an insect trigger and who underwent VIT incurred those additional costs (see *Table 24*, parameters 36–40). Model estimates on current practice of VIT in the UK are based on an audit that evaluated the adherence to international guidelines[48] and on expert opinion (Dr Pamela Ewan, Allergy Department, Addenbrookes Hospital, 9 June 2011, personal communication). Most of the VITs in the UK were given by injection of a purified extract (Pharmalgen, ALK-Abelló UK, Reading, UK), using an

TABLE 24 Cost parameters

No.	Parameter	Name of parameter in model	Distribution type	Low (triangular)	Mean (normal) or most likely (triangular)	Standard error (normal) or high (triangular)	Sources
33	Mean cost of inpatient care	dcostrecur	Normal	N/A	£469.88	37.585	*NHS Reference Costs 2009/10*[47]
34	Mean cost of AI	cinjector	N/A	N/A	£28.97	N/A	BNF 61[18]
35	Costs of SS sessions	cSS	N/A	N/A	(initial, follow-up) Children (£266, £234) Adults (£321, £450)	N/A	*NHS Reference Costs 2009/10*[47]
36	Duration of VIT (months)	ddurationVIT	Triangular	2	3	4	Based on Diwakar 2008[48]
37	Induction phase of VIT (build-up) (weeks)	dbuildupVIT	Triangular	8	10	12	Based on Cox *et al.* 2011[25] Expert opinion
38	Average cost for bee and wasp extract for VIT maintenance treatment	cVITmaintenance	N/A	N/A	£60	N/A	BNF 61[18]
39	Average cost for bee and wasp extract for VIT induction treatment	cVITinitial	N/A	N/A	£70	N/A	BNF 61[18]
40	No. of weeks between VIT maintenance doses	dnVITmaint	N/A	4	6	8	Expert opinion Cox *et al.* 2011[25]
41	Cost of prednisolone per milligram	cpred	N/A	N/A	0.02	N/A	BNF 61[18]
42	Duration of prednisolone course in months	ddurationpred	Uniform	2	N/A	3	Simons *et al.* 2010[27]
43	Start dose of prednisolone (mg)	dstartdosepred	Uniform	60	N/A	100	Simons *et al.* 2010,[27] Lieberman *et al.* 2010[24]

continued

TABLE 24 Cost parameters (*continued*)

No.	Parameter	Name of parameter in model	Distribution type	Low (triangular)	Mean (normal) or most likely (triangular)	Standard error (normal) or high (triangular)	Sources
44	Duration of start dose of prednisolone	dstartduration	Uniform	1	N/A	2	Simons *et al.* 2010,[27] Lieberman *et al.* 2010[24]
45	No. of follow-ups per year for those with a food trigger	nFUfoodSS	N/A	N/A	0.5	N/A	Expert opinion
46	Cost of follow-up for those with a food trigger	cFUfoodSS	N/A	N/A	£200	N/A	Expert opinion
47	Cost of VIT visit	cVITvisit	N/A	N/A			

N/A, not applicable.

induction scheme of weekly injection for about 10 weeks and continuation for about 3 years, with about a 6-weekly interval during maintenance.[48] In the model, a mean duration time of VIT of 3 years with a range of 2–4 years is used[48] (see *Table 24*, parameter 36). The average costs for bee and wasp extracts used for VIT were based on the costs reported in BNF 61[18] (parameter 38–39). The number of weeks between VIT maintenance doses was based on expert opinion and on the American guideline for allergen immunotherapy[25] (see *Table 24*, parameter 40). The duration of the build-up phase, based on expert opinion, was up to 10 weeks and, given that the next dose would not occur for at least another 4 weeks, implied that the cost in the first 3-month cycle was only that of initial treatment (£70). The cost thereafter is therefore calculated as number of maintenance doses multiplied by cost of maintenance dose (£60), where mean number of maintenance doses is duration of maintenance divided by number of weeks between doses.

Only those with idiopathic anaphylaxis with frequent episodes incurred the additional cost of prednisolone (see *Table 24*, parameters 41–44). The recommendation from two international guidelines[23,24] for prednisolone is 1–2 weeks every day, starting at 60–100 mg, until symptoms are under control and then decreasing over a period of about 2–3 months.

Those with food triggers also incurred additional regular follow-up costs in accordance with expert opinion that would be necessary to reinforce avoidance measures. According to expert opinion, the frequency would vary depending on the specific food trigger and age, with milk trigger in children having the highest frequency. However, an average of about once every 2 years over a lifetime was assumed in the base case (see *Table 24*, parameter 45). The cost of each follow-up was also taken from the NHS reference costs[47] (see *Table 24*, parameter 46).

Discount rate

The discount rate for costs and benefits was 3.5% in accordance with NICE methods guidance.[16]

General model assumptions

We assumed that 50% of the population consisted of males, which is based on the HES.[32] Furthermore, we assumed that there are only four main triggers of anaphylaxis: drug, food, insect/venom and idiopathic

(no known cause). We expected that in SC there is either no referral to SSs or a GP referral only after anaphylaxis, and that SSs essentially consisted of SC plus referral to SSs on the basis that the patient would probably see his/her GP as well. We also assumed, based on expert opinion, that anyone with anaphylaxis gets only two sessions with SSs unless cause of anaphylaxis is insect or idiopathic. In all causes, patients receive benefit from recurrence rate reduction, utility increase and mortality rate reduction from SSs, and from only mortality rate reductions with AI. We assumed that historic recurrence and mortality rates are due to SC only, given the likely low rate of referral to SSs: in one study the referral rate was zero.[13] Finally, we expected the cost of recurrence to be due to hospital admission only, i.e. no further follow-up costs were included, which is conservative in terms of the chances of SSs being cost-effective.

Further assumptions are explained in each of the sections on model parameters below.

Time horizon

The time horizon was lifetime in accordance with NICE methods guidance.[20]

Results

Base-case results

An arbitrary age of 30 years was chosen for the base case, and *Table 25* and *Figure 3* show the results of the model run probabilistically (10,000 simulations).

This shows that SC with AI would not be cost-effective. SS with no AI would be cost-effective if the threshold [willingness to pay (WTP) for a QALY] was greater than about £740, and SS with AI would be cost-effective if the threshold was >£1800 per QALY. Given a threshold of £20,000 this would make SS with AI cost-effective.

In order to show the effect of the uncertainty a cost-effectiveness acceptability curve (CEAC) was plotted.

Figure 4 shows that, at a threshold above about £2000 per QALY, SS with AI is most likely to be cost-effective, and, below this, SS without AI would be most likely.

Table 26 shows the results of the deterministic (parameters at expected values) analysis.

It can easily be seen that there is virtually no difference between the results, indicating that the expected cost and QALYs are close to a linear function of the parameter values. It is for this reason and that it is much quicker to run the TreeAge software deterministically that all one way or threshold sensitivity analyses were conducted deterministically.

TABLE 25 Base-case results (probabilistic)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost-effectiveness	Incremental cost-effectiveness (ICER)
SC no AI	981.13		39.22		25.02	
SS no AI	1744.40	763.27	40.25	1.03	43.34	742.01
SC plus AI	1879.96	135.56	39.76	–0.48	47.28	Dominated
SS plus AI	2668.52	924.12	40.76	0.51	65.47	1819.82

ICER, incremental cost-effectiveness ratio.

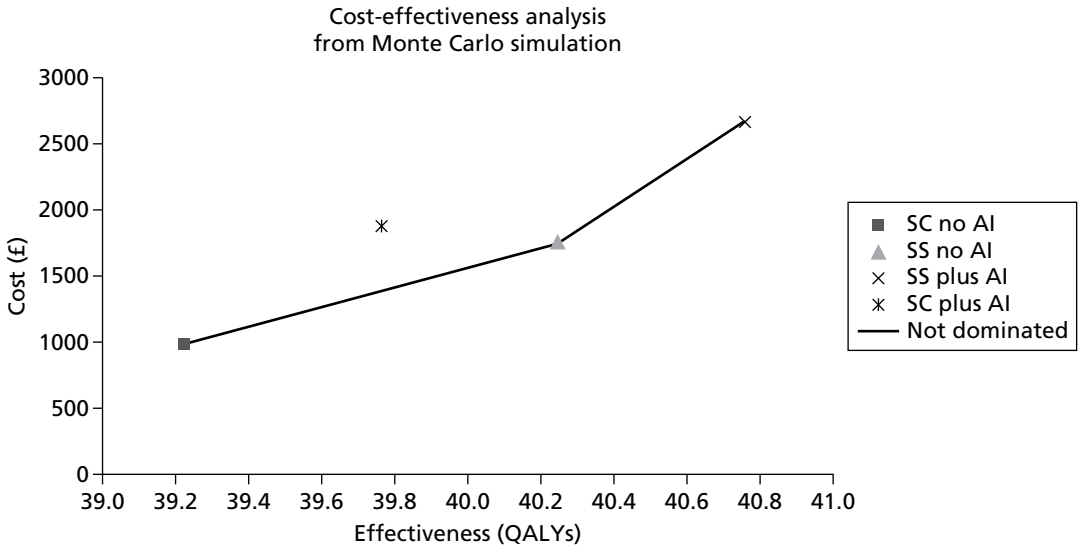

FIGURE 3 Base-case results (probabilistic).

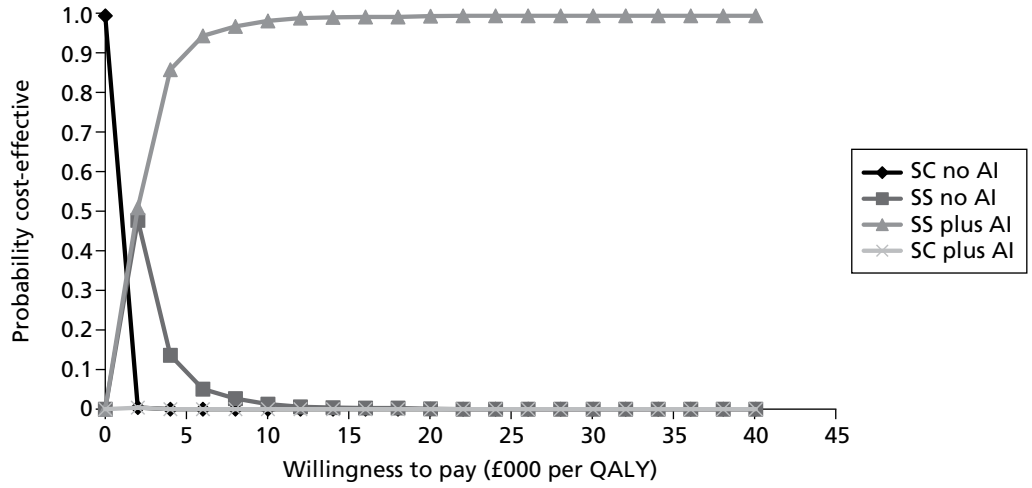

FIGURE 4 Cost-effectiveness acceptability curve: base case.

TABLE 26 Base-case results (deterministic)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost-effectiveness	Incremental cost-effectiveness (ICER)
SC no AI	978.26		39.25		24.93	
SS no AI	1745.19	766.93	40.25	1.00	43.36	763.45
SC plus AI	1875.83	130.64	39.79	–0.46	47.14	Dominated
SS plus AI	2668.59	923.40	40.76	0.51	65.47	1808.13

Sensitivity analysis

Table 27 shows the results for the age of 5 years.

The results are essentially very similar to those for the age of 30 years, except that SC plus AI was extendedly dominated [incremental cost-effectiveness ratio (ICER) to move from SC no AI is greater than to move from SC plus AI to SS no AI].

Table 28 shows the effect of varying the time horizon instead of using a lifetime.

Table 28 shows that, as the time horizon decreases, SSs plus AI becomes less likely to be cost-effective. Indeed, threshold analysis (see next paragraph) reveals that, starting at the age of 30 years, for a range of time horizons from 1 to 3 years, assuming a WTP of £20,000 per QALY, SC plus AI would be cost-effective. This is true up to 2 years only for children.

Threshold analysis was conducted on all parameters. All probabilities were varied between 0 and 1 and, unless stated otherwise, a WTP of £20,000 was used.

No change to SS plus AI being cost-effective was observed for the following:

- Population age (0–90 years, base case: 30 years).
- Probability trigger was drug.

TABLE 27 Results at age 5 years (base case: age 30 years)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost-effectiveness	Incremental cost-effectiveness (ICER)
SC no AI	1137.78		61.05		18.64	
SC plus AI	2551.18	1413.40	61.96	0.91	41.18	Extendedly dominated
SS no AI	3049.38	1911.60	62.96	1.91	48.44	999.94
SS plus AI	4501.53	1452.15	63.74	0.78	70.62	1850.46

TABLE 28 Time horizon 2 years (base case: lifetime)

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	Cost-effectiveness	Incremental cost-effectiveness (ICER)
Start age 30 years						
SC no AI	108.26		1.68		64.33	
SC plus AI	179.48	71.22	1.71	0.02	105.20	3076.31
SS no AI	919.95	740.47	1.70	0.00	539.72	Dominated
SS plus AI	992.17	812.69	1.73	0.02	574.19	37,207.02
Start age 5 years						
SC no AI	111.48		1.88		59.23	
SC plus AI	253.83	142.34	1.91	0.02	133.20	6110.20
SS no AI	685.84	432.01	1.90	0.00	360.27	Dominated
SS plus AI	830.21	576.38	1.93	0.02	430.79	26,689.05

- Probability trigger was idiopathic.
- Probability trigger was insect.
- Rate of recurrence with drug caused anaphylaxis with SC (base case: 0.12).
- Rate of recurrence with drug caused anaphylaxis with SS (up to 0.12, base case: 0.001).
- All rates of recurrence due to some trigger (drug, food or insect) with SSs (up to 10 times base case for all in multiway sensitivity analysis).
- Cost of SSs (up to £10,000, base case: about £250 or about £400, depending on age)
- Frequency of follow-up for food trigger (up to once per month, base case once every 2 years).
- Proportion frequent idiopathic.
- Probability of remission, either frequent or infrequent.
- Cost per milligram of prednisolone (up to £1, base case: £0.02).
- Cost of VIT (initial or maintenance) (up to £200).
- Effectiveness of VIT (0–1, base case: 0.85).
- Probability of correct use with SSs (0–1, base case: 0.9).
- Probability of dying from anaphylaxis with no intervention.
- Utility improvement factor for SSs (0–0.5, base case: 0.25).
- Utility improvement factor for AI (0–0.5, base case: 0.25).

It was observed that there was a change from:

SS plus AI to SC plus AI above 0.35 for rate of recurrence in food-caused anaphylaxis (base case: 0.01)

SS plus AI to SS no AI above 0.03 for probability of dying with injector (correct use) (base case: 0.000252)

SS plus AI to SS no AI above £146 for cost of injector (base case: £26.45) (at start age of 30 years; less than this implies a higher threshold)

SS plus AI to SS no AI below 0.03 for utility improvement factor with AI (base case: 0.25)

SS plus AI to SC plus AI between time horizon of about one and, for adults, 3 years and, for children, 2 years (base case: lifetime)

SS plus AI to SS no AI below 0.77 for probability of correct use with a SS, no utility increment for AI use (base case: 0.9)

Therefore, in summary, that SS plus AI was cost-effective at a threshold of £20,000 per QALY was robust to all sensitivity analysis except mostly at relatively extreme values of a small number of parameters. The only exception was if it was assumed that there was no benefit to having AIs irrespective of whether or not they were used correctly: this analysis was performed given the lack of evidence to inform the utility increment for AIs (see *Health valuation estimation*). In this case, a threshold of 0.77 (77%) does not seem that implausible.

Chapter 5 Assessment of factors relevant to the NHS and other parties

Given the conclusion that SSs are likely to be cost-effective, consideration would need to be given as to how to increase referral, such as by training or education. Also, any implementation would require an assessment of whether or not current SS capacity is sufficient if increased referral should occur.

Chapter 6 Discussion

Key results

The assessment of clinical effectiveness aimed to inform the following four questions:

- In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?
- What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause?
- What are the effects of providing adrenaline auto-injectors, including by whom?
- After assessment, when should referral take place?

The searches of electronic searches yielded 11,058 references. After screening of titles and abstracts, 10,951 references were excluded. The remaining 107 references were obtained and the full texts were screened. Five studies were included, none of which was a RCT. All five included studies were prospective observational studies reporting on risk of recurrence.[3–7] The studies, conducted in five countries (Australia, Germany, Italy, Spain and the USA), included 1725 patients overall.

Risk of recurrence was estimated to be between 30% and 42.8%. One study suggested the rate of a third event to be 5.2%, with a higher risk of recurrence for women (RR 2.14, 95% CI 1.17 to 3.9).[4] In children aged <12 years, an overall recurrence of 27% was reported, with food being the most frequent allergen (71%).[5] One larger study (432 patients) reported serious recurrences in 45 patients (10.4%), of whom 18 (40%) received adrenaline.[7]

The assessment of cost-effectiveness aimed to inform the following two questions:

- What are the cost-effectiveness of referral to specialist allergy clinics for the diagnosis of anaphylaxis (as opposed to for the acute event) and for the prevention of future episodes and the reduction in morbidity and mortality from future episodes?
- What is the cost-effectiveness of adrenaline auto-injectors for the treatment of anaphylaxis, including the cost implications of training in the use of the AI?

These two questions were translated into a comparison between four possible strategies:

1. SC plus no AI
2. SC plus AI
3. SS plus no AI
4. SS plus AI.

In order to avoid misunderstanding, the question was not the consequences of a change in current service configuration where there is a non-zero level of referral to SSs, i.e. there was a choice of either SC (with no SSs) or SSs. Furthermore, the population was those with a diagnosis of anaphylaxis and, therefore, did not include the possibility of misdiagnosis.

The effectiveness of AIs was mediated through reduction in mortality and a small utility improvement owing to reassurance. The effectiveness and cost reduction due to SSs was mediated through reduction in rate of recurrence and also a small utility improvement. The reduction in rate of recurrence was mediated

through mechanisms that depended on trigger: avoidance of trigger with drug and food and remission with insect and idiopathic.

A Markov model was constructed to model the possibility of recurrence over a lifetime in each of the subgroups by cause of anaphylaxis: insect, food, drug and idiopathic. It modelled the effect of SSs in terms of rate reduction via a mechanism that depended on the trigger, assuming that all patients had anaphylaxis and that the trigger was identified with certainty. AI (prescription of two injectors) effect was modelled as having an effect only on mortality due to recurrence. The results showed that, in the base case of a lifetime horizon, with a discount rate of 3.5%, SS with AI had an ICER of about £1800 (model run probabilistically or deterministically, i.e. all parameters set at expected value) and, therefore, would be cost-effective according to a threshold of no less than this figure. Any SC strategy (with or without AI) was dominated, i.e. found to be less effective and more costly than another strategy. SS with no AI would be cost-effective only below a threshold of about £740. The CEAC also revealed that above a WTP of about £2000, SS plus AI was also the most likely (highest probability) strategy to be cost-effective.

Given the complexity of the model and much uncertainty in many parameters, extensive sensitivity analysis in the form of threshold analyses was performed. This revealed that, variation in most parameters would not change the strategy that would be cost-effective. Indeed, only relatively extreme values for rate of food-caused anaphylaxis following SSs could cause a change to SC. Similarly, only relatively extreme values for the cost of injector, probability of dying with the injector or utility improvement factor (essentially the proportion of the utility decrement due to living with the risk of anaphylaxis that would be restored as a result of prescription of an injector) could cause a change to SS with no injector.

Strengths

First, all systematic review methods were conducted in accordance with the standards of the Cochrane Handbook.[49] This included a comprehensive search to identify relevant studies and all included studies were appropriately quality assessed. For the CEA, the methods were those recommended in the NICE guidance,[20] particularly in terms of using a lifetime horizon, discount rate of 3.5%, QALYs and costs from the perspective of the NHS. Also, PSA was used to model the uncertainty in the parameter estimates.

Second, both the model structure and parameter estimates were validated by expert opinion by presentation to the GDG, including after feedback from stakeholders. In particular, either all parameter estimates were taken directly from the literature and confirmed by expert opinion or, where literature estimates were absent or deemed not good enough, expert opinion was sought in the form of the most likely value, as well as lowest and highest plausible.

Third, all uncertain parameter estimates were subjected to sensitivity analysis, using threshold analysis, in order to check how extreme they needed to be to change the strategy that would be cost-effective. Indeed, most parameters had no effect and the small number that did had to be at quite extreme values in order to change which strategy would be cost-effective at a threshold of £20,000 per QALY. This analysis was extended to examine the effect of probability of correct use of AIs given SSs, assuming no utility increment for use of AIs. In that case, a threshold of 0.77 (base case: 0.9) was found, which might be interpreted as showing that the probability of correct use with SSs has to be 'quite high' or the addition of AIs might not be cost-effective. Of course, what counts as 'quite high' is subjective and the judgement of the experts was that 0.8 was the lowest possible value. However, this might be biased.

Fourth, the analysis takes appropriate account of inappropriate use of AIs by costing all prescriptions, but only incurring benefit by mortality reduction with correct and timely use.

Finally, a review of the extant CEA literature revealed that the cost-effectiveness of SSs had never been estimated before. One study[9] had examined AI, but only in the general allergic population, as opposed to

those who have had anaphylaxis, and it had not estimated QALYs. Therefore, this is the first CEA in the area of anaphylaxis treatment.

Weaknesses

First, although a comprehensive search was undertaken to identify relevant studies (see *Chapter 3*, *Quantity and quality of research available*), only five studies were included (see *Chapter 3*, *Assessment of clinical effectiveness*). All of these studies are observational studies with low or medium risk of bias assessing the risk of recurrence [and 'very low' quality of evidence using the GRADE approach, as detailed in *Chapter 3* (see *Results*)]. The studies were relatively small (1725 patients) and assessed the risk of recurrence in various patient groups. This limitation should be taken account when formulating recommendations based on these studies.

Second, no studies addressing any of the other clinical research questions in terms of history-taking, physical examination, provision of adrenaline auto-injectors, or referral to specialist allergy clinics for those with anaphylaxis were identified.

Third, in terms of the cost-effectiveness model, although validation by expert opinion did occur, several assumptions were made and, although parameter values were obtained, many did rely on expert opinion. This might also be said to be subject to 'bias', but, by definition, it can only be subjective and was obtained by involving the whole GDG, which is, through NICE, intended to be independent (www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/guidelinedevelopmentgroups/guideline_development_groups.jsp). Also, there was no attempt to either elicit individual GDG uncertainty or use a formal consensus process. However, in most cases, there was no threshold at which the strategy that is cost-effective would change. For example, the proportion of incident cases that were idiopathic was estimated from study of routine UK data[15] to be about 30%, but this did not differentiate by age. Two other UK studies were found that did differentiate cause by age[13,36,50] but it was not clear how many had idiopathic cause, although the proportion with 'aetiology not recorded' was about 34% (children 27% and adults 35%) in one study[50] and 'allergen not documented' 40% for both adults and children in the other.[36] Also, variation of this proportion by itself had no effect on the cost-effective strategy.

Many assumptions and several sources of data were required in order to estimate the mortality effect of AIs. However, only if the probability of dying with AI was raised above 0.03 (about 10 times that in the base case) would prescription of AI not be cost-effective.

Also, there was no direct evidence for the influence of AI or SSs on utility, for example owing to an increase or decrease in anxiety, but even a factor of 0 for SSs or AI had no effect on which strategy was cost-effective.

Fourth, for recurrence, only cost of hospital treatment for anaphylaxis was included, but this was conservative in relation to the effect of rate reduction by SSs and, even if reduced to zero, it would not change which strategy was cost-effective. Cost of SSs might have been too low if any capital investment was required, but even raising it to the equivalent of about 50 sessions had no effect. The only cost parameter change that had a threshold was that of the injectors, which were costed using the BNF[18] at £26.45 per injector with two injectors (or four for children) at 12-monthly replacement. Only above an unrealistic £146, the strategy that would be cost-effective at an ICER threshold of £20,000 would be SS without injector.

Fifth, the population was limited to those confirmed to have a diagnosis of anaphylaxis. However, not only did the GDG consider this to be reasonable, but misdiagnosis would most likely only waste cost, the effect of which was tested by variation in cost of SSs. There were also no parameters for tests for trigger

identification, but any misidentification would only have decreased effectiveness, which was tested by variation in rate of recurrence with SSs.

Sixth, cost of training in the use of AIs was not explicitly included, but expert opinion was that this could be included in the SS cost; including an extra cost with SC would only have made it less likely to be cost-effective.

Finally, the evidence used for effectiveness of SS management to reduce risk of recurrence was also very sparse, and the rate of recurrence for drug-caused anaphylaxis with SC was believed by some stakeholders to be too high. However, variation in this parameter, effectiveness of VIT or probability of remission in idiopathic anaphylaxis had no effect. It is also possible that remission might occur not only in the idiopathic group. However, in the World Allergy Organization Guidelines, published this year,[23] remission is mentioned only as a possibility in idiopathic anaphylaxis. Also, the net effect of remission might not make much difference. On the one hand it would improve health outcomes of SC relative to SSs, but, on the other hand, it would also decrease the cost of SSs relative to SC as a result of reduced need for follow-up. Moreover, only raising the rate of recurrence from 0.01 to 0.35 (35 times the base case) for food cause would make SC cost-effective.

Generalisability

The results of the clinical evidence review are generally applicable. Also, overall model structure, insofar as it models the natural history of those at risk of anaphylaxis and to some extent the health-related parameter values, such as rate of recurrence with SC, will be generalisable across settings and countries. However, many parameter values, such as the probability that anaphylaxis has a particular trigger and the rates of recurrence given SSs, as well as costs, will probably be particular to the nature of health services in the UK. Therefore, the results are unlikely to be generalisable beyond the UK.

Chapter 7 Conclusions

The systematic review revealed only five studies addressing risk of recurrence. No study was found that directly addressed any of the other clinical research questions in terms of history-taking, physical examination, provision of adrenaline auto-injectors, or referral to specialist allergy clinics for those with anaphylaxis. None of the included studies was a RCT.

The results of the CEA showed that SS with AI was cost-effective at a threshold of £20,000 per QALY. However, given the lack of RCTs, the model had to be informed by observational studies and expert opinion.

Given that the results that both referral to a SS and prescription of AIs are likely to be cost-effective and that this study has been used to inform a NICE guideline, it does potentially have important implications for policy. The guideline was published in December 2011.

In addition, the lack of good data to inform the effectiveness by any measure of any anaphylaxis intervention means that we recommend consideration of RCTs, or at least well-designed observational studies, of the components of care in SSs. These components include all those that formed the CEA model, including AIs, trigger avoidance measures, VIT and idiopathic anaphylaxis treatment.

Acknowledgements

Contribution of authors

Nigel Armstrong (Health Economist, KSR) led the CEA and wrote this section of the report.

Robert Wolff (Systematic Reviewer, KSR) led the systematic review and wrote this section of the report.

Ghislaine van Mastrigt (Health Economist, Maastricht, the Netherlands) contributed to the CEA and the writing of the report.

Nahara Martinez (Systematic Reviewer, Zurich, Switzerland) and Adrian V Hernandez (Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA) were involved in screening of title, abstracts, and full texts and preparation of GRADE summary of findings tables.

Kate Misso formulated the search strategies, carried out searches and wrote this section of the report.

Jos Kleijnen (Director, KSR) supervised the project.

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Appendix 1 Literature search strategies

Systematic reviews and mapping searches

What are the effects of history-taking, including signs and symptoms, and physical examination in identifying the possible cause? (Clinical assessment and history-taking search.)

The clinical assessment search was conducted in February 2011.

MEDLINE (OvidSP): 1948 to week 1 February 2011

Searched 16 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83,258)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15,288)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24,149)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (4316)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (2250)
6. or/1-5 (105,987)
7. exp Emergency Treatment/ (80,137)
8. (Accident adj2 emergency).ti,ab,ot,hw. (3474)
9. exp Emergency Medical Services/ (75,543)
10. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or interven$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (115,106)
11. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or interven$ or therap$ or patient$)).ti,ab,ot,hw. (823)
12. (Accident adj2 emergency).ti,ab,ot,hw. (3474)
13. Triage$.ti,ab,ot,hw. (9800)
14. First aid$.ti,ab,ot,hw. (8194)
15. (First response$ or first respond$).ti,ab,ot,hw. (1533)
16. (Medical adj2 urgen$).ti,ab,ot,hw. (423)
17. Emergencies/ (30,977)
18. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (374)
19. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (530)
20. or/7-19 (213,695)
21. Physical Examination/ (25,045)
22. ((clinical$ or physical$) adj2 (assess$ or exam$ or test$ or history or histories)).ti,ab,ot,hw. (166,918)
23. exp medical history taking/ or cornell medical index/ (16,109)
24. ((Medical$ or patient$) adj2 (histories or history)).ti,ab,ot,hw. (38,080)
25. Anamnesis.ti,ab,ot,hw. (3349)
26. ((identif$ or trace$ or tracing or track$ or locat$ or post$ or isolat$ or pinpoint$ or pin-point$ or ascertain$ or detect$ or distinguish$ or recognis$ or recogniz$ or associate$ or connect$ or equat$ or

link$ or discover$ or find$ or name$ or naming or investigat$) adj2 (causal$ or cause$ or causation$ or trigger$ or reason$ or source$ or sensitive$ or hypersensitive$ or allerg$)).ti,ab,ot,hw. (65,478)
27. exp skin tests/ (50,471)
28. (allerg$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (1982)
29. (Sensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (80,112)
30. (hypersensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (334)
31. ((skin or intradermal$ or intra-dermal$ or intracutaneous$ or epidermal$ or cutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (40,005)
32. ((passive transfer or prausnitz kustner or kveim) adj2 (test$ or investigat$)).ti,ab,ot,hw. (434)
33. (RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (1171)
34. (prick adj1 (test$ or investigat$)).ti,ab,ot,hw. (6231)
35. ((patch or percutaneous$ or epicutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (10,447)
36. (CAP RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (22)
37. (specific IgE adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (415)
38. Fluorenzymeimmunoassay$.ti,ab,ot,hw. (0)
39. (Pharmacia CAP adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (19)
40. (radioallergosorben$ adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (4428)
41. (radioimmunoassay$ adj2 (test or investigat$)).ti,ab,ot,hw. (316)
42. ((ImmunoCAP or Immuno-CAP) adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (40)
43. Skin end point titration.ti,ab,ot,hw. (13)
44. rinkel serial dilution titration.ti,ab,ot,hw. (1)
45. Challenge test$.ti,ab,ot,hw. (4140)
46. (mast cell tryptase adj2 (test$ or assay$ or investigat$)).ti,ab,ot,hw. (5)
47. or/21-46 (402,839)
48. 6 and 20 and 47 (271)
49. animals/ not (animals/ and humans/) (3,403,655)
50. 48 not 49 (268)

Medline In-Process Citations (OvidSP): up to 15 February 2011
Medline Daily Update (OvidSP): up to 15 February 2011

Searched 16 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (72)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (18)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (589)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (179)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (100)
6. or/1-5 (860)
7. exp Emergency Treatment/ (111)
8. (Accident adj2 emergency).ti,ab,ot,hw. (66)
9. exp Emergency Medical Services/ (129)
10. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or interven$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (4365)
11. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or interven$ or therap$ or patient$)).ti,ab,ot,hw. (21)
12. (Accident adj2 emergency).ti,ab,ot,hw. (66)

13. Triage$.ti,ab,ot,hw. (398)
14. First aid$.ti,ab,ot,hw. (124)
15. (First response$ or first respond$).ti,ab,ot,hw. (87)
16. (Medical adj2 urgen$).ti,ab,ot,hw. (24)
17. Emergencies/ (13)
18. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (18)
19. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (38)
20. or/7-19 (4984)
21. Physical Examination/ (32)
22. ((clinical$ or physical$) adj2 (assess$ or exam$ or test$ or history or histories)).ti,ab,ot,hw. (6253)
23. exp medical history taking/ or cornell medical index/ (17)
24. ((Medical$ or patient$) adj2 (histories or history)).ti,ab,ot,hw. (1291)
25. Anamnesis.ti,ab,ot,hw. (85)
26. ((identif$ or trace$ or tracing or track$ or locat$ or post$ or isolat$ or pinpoint$ or pin-point$ or ascertain$ or detect$ or distinguish$ or recognis$ or recogniz$ or associate$ or connect$ or equat$ or link$ or discover$ or find$ or name$ or naming or investigat$) adj2 (causal$ or cause$ or causation$ or trigger$ or reason$ or source$ or sensitive$ or hypersensitive$ or allerg$)).ti,ab,ot,hw. (4210)
27. exp skin tests/ (33)
28. (allerg$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (61)
29. (Sensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (343)
30. (hypersensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (3)
31. ((skin or intradermal$ or intra-dermal$ or intracutaneous$ or epidermal$ or cutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (432)
32. ((passive transfer or prausnitz kustner or kveim) adj2 (test$ or investigat$)).ti,ab,ot,hw. (1)
33. (RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (9)
34. (prick adj1 (test$ or investigat$)).ti,ab,ot,hw. (206)
35. ((patch or percutaneous$ or epicutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (188)
36. (CAP RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (0)
37. (specific IgE adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (11)
38. Fluorenzymeimmunoassay$.ti,ab,ot,hw. (0)
39. (Pharmacia CAP adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (0)
40. (radioallergosorben$ adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (12)
41. (radioimmunoassay$ adj2 (test or investigat$)).ti,ab,ot,hw. (3)
42. ((ImmunoCAP or Immuno-CAP) adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (4)
43. Skin end point titration.ti,ab,ot,hw. (0)
44. rinkel serial dilution titration.ti,ab,ot,hw. (0)
45. Challenge test$.ti,ab,ot,hw. (129)
46. (mast cell tryptase adj2 (test$ or assay$ or investigat$)).ti,ab,ot,hw. (0)
47. or/21-46 (12,625)
48. 6 and 20 and 47 (4)
49. animals/ not (animals/ and humans/) (2774)
50. 48 not 49 (4)

EMBASE (OvidSP): 1980 to week 6 2011

Searched 17 February 2011

1. Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (87,798)
2. Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18,305)
3. Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32,758)

4. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (39,238)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (5910)
6. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (3040)
7. or/1-6 (136,815)
8. animal/ or animal experiment/ (3,045,231)
9. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,666,017)
10. or/8-9 (4,666,017)
11. exp human/ or human experiment/ (12,216,815)
12. 10 not (10 and 11) (3,748,300)
13. 7 not 12 (122,765)
14. EMERGENCY/ (24,427)
15. emergency treatment/ or evidence based emergency medicine/ or first aid/ or pediatric advanced life support/ (20,946)
16. emergency care/ (10,408)
17. Emergency-Medicine/ (16,466)
18. Emergency-Health-Service/ (50,147)
19. Emergency-Patient/ (545)
20. Emergency-Ward/ (31,998)
21. (Accident adj2 emergency).ti,ab,ot,hw. (3937)
22. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or interven$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (146,375)
23. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or interven$ or therap$ or patient$)).ti,ab,ot,hw. (956)
24. Triage$.ti,ab,ot,hw. (8325)
25. First aid$.ti,ab,ot,hw. (10,473)
26. (First response$ or first respond$).ti,ab,ot,hw. (1748)
27. (Medical adj2 urgen$).ti,ab,ot,hw. (559)
28. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (425)
29. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (800)
30. or/14-29 (184,896)
31. clinical assessment/ (33,978)
32. Physical Examination/ (94,953)
33. Medical-History/ or anamnesis/ (104,176)
34. Allergy-Test/ (2167)
35. ((clinical$ or physical$) adj2 (assess$ or exam$ or test$ or history or histories)).ti,ab,ot,hw. (320,112)
36. ((Medical$ or patient$) adj2 (histories or history)).ti,ab,ot,hw. (34,556)
37. Anamnesis.ti,ab,ot,hw. (103,947)
38. ((identif$ or trace$ or tracing or track$ or locat$ or post$ or isolat$ or pinpoint$ or pin-point$ or ascertain$ or detect$ or distinguish$ or recognis$ or recogniz$ or associate$ or connect$ or equat$ or link$ or discover$ or find$ or name$ or naming or investigat$) adj2 (causal$ or cause$ or causation$ or trigger$ or reason$ or source$ or sensitive$ or hypersensitive$ or allerg$)).ti,ab,ot,hw. (80,772)
39. (allerg$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (4268)
40. (Sensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (7328)
41. (hypersensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (366)

42. ((skin or intradermal$ or intra-dermal$ or intracutaneous$ or epidermal$ or cutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (38,783)
43. ((passive transfer or prausnitz kustner or kveim) adj2 (test$ or investigat$)).ti,ab,ot,hw. (440)
44. (RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (1246)
45. (prick adj1 (test$ or investigat$)).ti,ab,ot,hw. (12,367)
46. ((patch or percutaneous$ or epicutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (14,561)
47. (CAP RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (27)
48. (specific IgE adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (614)
49. Fluorenzymeimmunoassay$.ti,ab,ot,hw. (0)
50. (Pharmacia CAP adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (22)
51. (radioallergosorben$ adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (5582)
52. (radioimmunoassay$ adj2 (test or investigat$)).ti,ab,ot,hw. (320)
53. ((ImmunoCAP or Immuno-CAP) adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (75)
54. Skin end point titration.ti,ab,ot,hw. (17)
55. rinkel serial dilution titration.ti,ab,ot,hw. (1)
56. Challenge test$.ti,ab,ot,hw. (5290)
57. (mast cell tryptase adj2 (test$ or assay$ or investigat$)).ti,ab,ot,hw. (8)
58. or/31-57 (556,805)
59. 13 and 30 and 58 (621)
60. animal/ or animal experiment/ (3,045,231)
61. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,666,017)
62. or/60-61 (4,666,017)
63. exp human/ or human experiment/ (12,216,815)
64. 62 not (62 and 63) (3,748,300)
65. 59 not 64 (621)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 1:2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011
http://cochranelibrary.com/

Searched 18 February 2011

1. Medical subject heading (MeSH) descriptor Hypersensitivity, this term only (525)
2. MeSH descriptor Anaphylaxis, this term only (142)
3. MeSH descriptor Asthma, Aspirin-Induced explode all trees (0)
4. MeSH descriptor Drug Hypersensitivity, this term only (403)
5. MeSH descriptor Drug Eruptions explode all trees (353)
6. MeSH descriptor Eosinophilic Esophagitis, this term only (0)
7. MeSH descriptor Hypersensitivity, Immediate, this term only (382)
8. MeSH descriptor Food Hypersensitivity, this term only (381)
9. MeSH descriptor Alveolitis, Extrinsic Allergic, this term only (11)
10. MeSH descriptor Latex Hypersensitivity, this term only (28)
11. MeSH descriptor Aspergillosis, Allergic Bronchopulmonary, this term only (11)
12. (anaphyla* OR pseudoanaphyla*):ti,ab,kw (533)
13. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near3 (allerg* or hypersensiti* or hypersensiti*)):ti,ab,kw (409)
14. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near2 (systemic* or allerg* or skin* or dermatolog* or cutaneous*) near2 (reaction* or effect* or event* or rash*)):ti,ab,kw (107)
15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (2810)

16. MeSH descriptor Emergency Treatment explode all trees (3357)
17. (Accident near2 emergency):ti,ab,kw (203)
18. MeSH descriptor Emergency Medical Services explode all trees (2535)
19. (Emergenc* near3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room* or rooms or care or medic* or interven* or therap* or hospital* or service*)):ti,ab,kw (5781)
20. (Casualty near2 (department* or admit* or admission* or patient* or case* or care or medicat* or interven* or therap* or patient*)):ti,ab,kw (35)
21. (Accident near2 emergency):ti,ab,kw (203)
22. Triage*:ti,ab,kw (435)
23. (First near1 aid*):ti,ab,kw (122)
24. (First near1 respons*):ti,ab,kw (247)
25. (First near1 respond*):ti,ab,kw (111)
26. (Medical near2 urgen*):ti,ab,kw (12)
27. MeSH descriptor Emergencies, this term only (609)
28. (postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*):ti,ab,kw (39)
29. (post near (episod* or admission* or admit* or reaction* or event* or incident*)):ti,ab,kw (519)
30. (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29) (10,188)
31. MeSH descriptor Physical Examination, this term only (678)
32. MeSH descriptor Skin Tests explode all trees (1878)
33. ((clinical* or physical*) near2 (assess* or exam* or test* or history or histories)):ti,ab,kw (11,235)
34. MeSH descriptor Medical History Taking explode all trees (265)
35. MeSH descriptor Cornell Medical Index, this term only (6)
36. ((Medical* or patient*) near2 (histories or history)):ti,ab,kw (1003)
37. Anamnesis:ti,ab,kw (128)
38. ((identif* or trace* or tracing or track* or locat* or post* or isolat* or pinpoint* or pin-point* or ascertain* or detect* or distinguish* or recognis* or recogniz* or associate* or connect* or equat* or link* or discover* or find* or name* or naming or investigat*) near2 (causal* or cause* or causation* or trigger* or reason* or source* or sensitive* or hypersensitive* or allerg*)):ti,ab,kw (1736)
39. (allerg* near1 (test* or investigat*)):ti,ab,kw (98)
40. (Sensitivit* near1 (test* or investigat*)):ti,ab,kw (1883)
41. (hypersensitivit* near1 (test* or investigat*)):ti,ab,kw (33)
42. ((skin or intradermal* or intra-dermal* or intracutaneous* or epidermal* or cutaneous*) near1 (test* or investigat*)):ti,ab,kw (2269)
43. ((passive transfer or prausnitz kustner or kveim) near2 (test* or investigat*)):ti,ab,kw (3)
44. (RAST near2 (test or assay* or investigat*)):ti,ab,kw (87)
45. (prick near1 (test* or investigat*)):ti,ab,kw (685)
46. ((patch or percutaneous* or epicutaneous*) near1 (test* or investigat*)):ti,ab,kw (514)
47. (CAP RAST near2 (test or assay* or investigat*)):ti,ab,kw (2)
48. (specific IgE near2 (test or assay* or investigat*)):ti,ab,kw (50)
49. Fluorenzymeimmunoassay*:ti,ab,kw (0)
50. (Pharmacia CAP near2 (test or assay* or investigat*)):ti,ab,kw (1)
51. (radioallergosorben* near2 (test or assay* or investigat*)):ti,ab,kw (188)
52. (radioimmunoassay* near2 (test or investigat*)):ti,ab,kw (50)
53. ((ImmunoCAP or Immuno-CAP) near2 (test or assay* or investigat*)):ti,ab,kw (3)
54. Skin end point titration:ti,ab,kw (30)
55. rinkel serial dilution titration:ti,ab,kw (1)
56. Challenge test*:ti,ab,kw (4139)
57. (mast cell tryptase near2 (test* or assay* or investigat*)):ti,ab,kw (1)
58. (#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45) (18,252)

59. (#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58) (21,882)
60. (#15 AND #30 AND #59) (6)

The CDSR search retrieved zero records.

The CENTRAL search retrieved six records.

Database of Abstracts of Reviews of Effects (DARE) (Internet): 2000 to 17 February 2011
Health Technology Assessment (HTA) (Internet): 2000 to 17 February 2011
NHS Economic Evaluation Database (NHS EED) (Internet): 2000 to 17 February 2011
www.crd.york.ac.uk/crdweb/

Searched 18 February 2011

1. MeSH Hypersensitivity (51)
2. MeSH Drug hypersensitivity (29)
3. MeSH Hypersensitivity, immediate (7)
4. MeSH Anaphylaxis (17)
5. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
6. MeSH food hypersensitivity (13)
7. MeSH alveolitis, extrinsic allergic (0)
8. MeSH aspergillosis, allergic bronchopulmonary (0)
9. MeSH latex hypersensitivity (5)
10. Anaphyla* OR pseudoanaphyla* (80)
11. (severe* NEAR allerg*) OR (severity NEAR allerg*) OR (worse* NEAR allerg*) OR (acute* NEAR allerg*) (117)
12. (emergenc* NEAR allerg*) OR (urgen* NEAR allerg*) OR (grave* NEAR allerg*) OR (serious* NEAR allerg*) (50)
13. (dangerous* NEAR allerg*) OR (life-threat* NEAR allerg*) OR (lifethreat* NEAR allerg*) OR (potentially AND fatal* NEAR allerg*) (12)
14. (severe* NEAR Hypersensiti*) OR (severity NEAR Hypersensiti*) OR (worse* NEAR Hypersensiti*) OR (acute* NEAR Hypersensiti*) (29)
15. (emergenc* NEAR Hypersensiti*) OR (urgen* NEAR Hypersensiti*) OR (grave* NEAR Hypersensiti*) OR (serious* NEAR Hypersensiti*) (11)
16. (dangerous* NEAR Hypersensiti*) OR (life-threat* NEAR Hypersensiti*) OR (lifethreat* NEAR Hypersensiti*) OR (potentially AND fatal* NEAR Hypersensiti*) (5)
17. (severe* NEAR Hyper-sensiti*) OR (severity NEAR Hyper-sensiti*) OR (worse* NEAR Hyper-sensiti*) OR (acute* NEAR Hyper-sensiti*) (29)
18. (emergenc* NEAR Hyper-sensiti*) OR (urgen* NEAR Hyper-sensiti*) OR (grave* NEAR Hyper-sensiti*) OR (serious* NEAR Hyper-sensiti*) (11)
19. (dangerous* NEAR Hyper-sensiti*) OR (life-threat* NEAR Hyper-sensiti*) OR (lifethreat* NEAR Hyper-sensiti*) OR (potentially AND fatal* NEAR Hyper-sensiti*) (5)
20. (severe* NEAR Systemic*) OR (severity NEAR Systemic*) OR (worse* NEAR Systemic*) OR (acute* NEAR Systemic*) (180)
21. (emergenc* NEAR Systemic*) OR (urgen* NEAR Systemic*) OR (grave* NEAR Systemic*) OR (serious* NEAR Systemic*) (41)
22. (dangerous* NEAR Systemic*) OR (life-threat* NEAR Systemic*) OR (lifethreat* NEAR Systemic*) OR (potentially AND fatal* NEAR Systemic*) (17)
23. (dangerous* NEAR Skin) OR (life-threat* NEAR Skin) OR (lifethreat* NEAR Skin) OR (potentially AND fatal* NEAR Skin) (14)

24. (severe* NEAR Skin) OR (severity NEAR Skin) OR (worse* NEAR Skin) OR (acute* NEAR Skin) (174)
25. (emergenc* NEAR Skin) OR (urgen* NEAR Skin) OR (grave* NEAR Skin) OR (serious* NEAR Skin) (85)
26. (severe* NEAR Dermatolog*) OR (severity NEAR Dermatolog*) OR (worse* NEAR Dermatolog*) OR (acute* NEAR Dermatolog*) (41)
27. (emergenc* NEAR Dermatolog*) OR (urgen* NEAR Dermatolog*) OR (grave* NEAR Dermatolog*) OR (serious* NEAR Dermatolog*) (7)
28. (dangerous* NEAR Dermatolog*) OR (life-threat* NEAR Dermatolog*) OR (lifethreat* NEAR Dermatolog*) OR (potentially AND fatal* NEAR Dermatolog*) (0)
29. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (520)
30. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (805)
31. Emergenc* OR Casualit* OR Accident* OR Triage* OR (First NEAR aid*) OR (first NEAR respond*) OR (first NEAR response*) OR (Medical NEAR urgen*) (2942)
32. (postepisod* OR postadmission* OR postadmit* OR postreaction* OR postevent* OR postincident*) (2)
33. episod* OR admission* OR admit* OR reaction* OR event* OR incident* (10,264)
34. #31 or #32 or #33 (11,899)
35. #30 and #34 (454)
36. (identif* OR trace* OR tracing OR track* OR locat* OR post* OR isolat* OR pinpoint* OR pin-point* OR ascertain* OR detect* OR distinguish* OR recognis* OR recogniz* OR associate* OR connect* OR equat* OR link* OR discover* OR find* OR name* OR naming OR investigat*) AND (causal* OR cause* OR causation* OR trigger* OR reason* OR source* OR sensitive* OR hypersensitive* OR allerg*) (15,013)
37. (Medical* NEAR history*) OR (patient* NEAR history*) OR Anamnesis (1297)
38. (clinical* NEAR assess*) OR (clinical* NEAR exam*) OR (clinical* NEAR test*) OR (clinical* NEAR histor*) (10,981)
39. (physical* NEAR assess*) OR (physical* NEAR exam*) OR (physical* NEAR test*) OR (physical* NEAR histor*) (1206)
40. Fluorenzymeimmunoassay* (0)
41. (allerg* OR hypersentiv* OR hyper-sensitiv* OR skin OR intradermal* OR intra-dermal* OR intracutaneous* OR epidermal* OR cutaneous*) AND (test* OR investigat*) (1257)
42. (passive AND transfer OR prausnitz AND kustner OR kveim OR RAST OR prick OR patch OR percutaneous* OR epicutaneous* OR IgE OR radioallergosorben* OR radioimmunoassay* OR ImmunoCAP OR Immuno-CAP OR rinkel OR challenge OR mast AND cell) AND (test* OR assay* OR investigat*) (803)
43. #36 or #37 or #38 or #39 or #40 or #41 or #42 (20,628)
44. #44 #35 and #43 (386)

The DARE search retrieved 205 records.

The NHS EED search retrieved 165 records.

The HTA search retrieved 16 records.

Science Citation Index (SCI) (Web of Science): 1970 to 12 February 2011

Searched 14 February 2011

32 503 #31 and #30
Databases = SCI-EXPANDED Timespan = All Years

31 1391 #6 and #13
Databases = SCI-EXPANDED Timespan = All Years

30 >100,000 #29 OR #28
Databases = SCI-EXPANDED Timespan = All Years

29 18,936 #21 or #22 or #23 or #24 or #25 or #26 or #27
Databases = SCI-EXPANDED Timespan = All Years

28 >100,000 #14 or #15 or #16 or #17 or #18 or #19 or #20
Databases = SCI-EXPANDED Timespan = All Years

27 275 TS = (mast cell tryptase SAME (test* or assay* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

26 38 TS = (rinkel serial dilution titration or Skin end point titration or challeng test*)
Databases = SCI-EXPANDED Timespan = All Years

25 92 TS = ((ImmunoCAP or Immuno-CAP) SAME (test or assay* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

24 1538 TS = ((radioimmunoassay* or radioallergosorben*) SAME (test or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

23 91 TS = (Pharmacia CAP SAME (test or assay* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

22 3155 TS = (specific IgE SAME (test or assay* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

21 14,235 TS = (((patch or percutaneous* or epicutaneous*) SAME (test* or investigat*)) or Fluorenzymeimmunoassay*)
Databases = SCI-EXPANDED Timespan = All Years

20 4189 TS = ((RAST or prick) SAME (test or assay* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

19 826 TS = ((passive transfer or prausnitz kustner or kveim) SAME (test* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

18 40,944 TS = ((skin or intradermal* or intra-dermal* or intracutaneous* or epidermal* or cutaneous*) SAME (test* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

17 75,193 TS = ((allerg* or Sensitivit* or hypersensitivit*) SAME (test* or investigat*))
Databases = SCI-EXPANDED Timespan = All Years

16 >100,000 TS = ((identif* or trace* or tracing or track* or locat* or post* or isolat* or pinpoint* or pin-point* or ascertain* or detect* or distinguish* or recognis* or recogniz* or associate* or connect* or equat* or link* or discover* or find* or name* or naming or investigat*) SAME (causal* or cause* or causation* or trigger* or reason* or source* or sensitive* or hypersensitive* or allerg*))
Databases = SCI-EXPANDED Timespan = All Years

15 74,293 TS = (((Medical* or patient*) SAME (histories or history)) or Anamnesis)
Databases = SCI-EXPANDED Timespan = All Years

14 >100,000 TS = ((clinical* or physical*) SAME (assess* or exam* or test* or history or histories))
Databases = SCI-EXPANDED Timespan = All Years

13 >100,000 #7 or #8 or #9 or #10 or #11 or #12
Databases = SCI-EXPANDED Timespan = All Years

12 13,113 TS = (post SAME (episod* or admission* or admit* or reaction* or event* or incident*))
Databases = SCI-EXPANDED Timespan = All Years

11 372 TS = (postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*)
Databases = SCI-EXPANDED Timespan = All Years

10 >100,000 TS = ((Medical SAME urgen*) or (First response* or first respond*))
Databases = SCI-EXPANDED Timespan = All Years

9 3039 TS = ((Triage*or First aid*) or (Accident SAME emergency))
Databases = SCI-EXPANDED Timespan = All Years

8 682 TS = (Casualty SAME (department* or admit* or admission* or patient* or case* or care or medicat* or interven* or therap* or patient*))
Databases = SCI-EXPANDED Timespan = All Years

7 71,359 TS = (Emergenc* SAME (treat* or admit* or admission* or episode* or case* or patient* or department* or room* or rooms or care or medic* or interven* or therap* or hospital* or service*))
Databases = SCI-EXPANDED Timespan = All Years

6 23,983 #4 not #5
Databases = SCI-EXPANDED Timespan = All Years

5 >100,000 TS = (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
Databases = SCI-EXPANDED Timespan = All Years

4 28,875 #1 or #2 or #3
Databases = SCI-EXPANDED Timespan = All Years

3 7739 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (systemic* or allerg* or skin* or dermatolog* or cutaneous*) SAME (reaction* or effect* or event* or rash*))
Databases = SCI-EXPANDED Timespan = All Years

2 8259 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (allerg* or Hypersensiti* or hyper-sensiti*))
Databases = SCI-EXPANDED Timespan = All Years

1 16,857 TS = (Anaphyla* or pseudoanaphyla*)
Databases = SCI-EXPANDED Timespan = All Years

Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost): 1981 to 18 February 2011

Searched 23 February 2011

S27 s14 and s26 Limiters - Exclude MEDLINE records (13)

S26 s15 or s16 or s17 or s18 or s19 or s20 or s21 or s22 or s23 or s24 or s25 (161,809)

S25 TX ((Skin N1 end N1 point N1 titration) or (rinkel N2 titration) or (Challenge N2 test*)) or TX ((mast N2 cell N2 test*) or (mast N2 cell N2 assay*) or (mast N2 cell N2 investigat*)) (498)

S24 TX ((CAP N2 test*) or (CAP N2 assay*) or (CAP N2 investigat*) or (IMMUNOCAP N2 test*) or (IMMUNOCAP N2 assay*) or (IMMUNOCAP N2 investigat*)) or TX ((radioallergosorben* N2 test*) or (radioallergosorben* N2 assay*) or (radioallergosorben* N2 investigat*)) or TX ((radioimmunoassay* N2 test*) or (radioimmunoassay* N2 assay*) or (radioimmunoassay* N2 investigat*)) (214)

S23 TX ((RAST N2 test*) or (RAST N2 assay*) or (RAST N2 investigat*)) or TX ((patch N1 test*) or (percutaneous* N1 test*) or (epicutaneous* N1 test*) or (patch N1 investigat*) or (percutaneous* N1 investigat*) or (epicutaneous* N1 investigat*)) or TX ((IgE N2 test*) or (IgE N2 assay*) or (IgE N2 investigat*) or Fluorenzymeimmunoassay*) (400)

S22 TX ((allerg* N1 test*) or (allerg* N1 investigat*) or (sensitivit* N1 test*) or (sensitivit* N1 investigat*) or (hypersensitivit* N1 test*) or (hypersensitivit* N1 investigat*)) or TX ((epidermal* N1 test*) or (epidermal* N1 investigat*) or (cutaneous* N1 test*) or (cutaneous* N1 investigat*)) or TX ((passive N1 transfer) or (prausnitz N1 kustner) or kveim or (prick N1 test*) or (prick N1 investigat*)) (6490)

S21 AB (identif* or trace* or tracing or track* or locat* or post* or isolat* or pinpoint* or pin-point* or ascertain* or detect* or distinguish* or recognis* or recogniz* or associate* or connect* or equat* or link* or discover* or find* or name* or naming or investigat*) and AB (causal* or cause* or causation* or trigger* or reason* or source* or sensitive* or hypersensitive* or allerg*) (91,791)

S20 TI (identif* or trace* or tracing or track* or locat* or post* or isolat* or pinpoint* or pin-point* or ascertain* or detect* or distinguish* or recognis* or recogniz* or associate* or connect* or equat* or link* or discover* or find* or name* or naming or investigat*) and TI (causal* or cause* or causation* or trigger* or reason* or source* or sensitive* or hypersensitive* or allerg*) (2143)

S19 TX (skin N1 test*) or (skin N1 investigat*) or (intradermal* N1 test*) or (intradermal* N1 investigat*) or (intra-dermal* N1 test*) or (intra-dermal* N1 investigat*) or (intracutaneous* N1 test*) or (intracutaneous* N1 investigat*) or (intra-cutaneous* N1 test*) or (intra-cutaneous* N1 investigat*) (2374)

S18 TX ((clinical* N2 assess*) or (clinical* N2 exam*) or (clinical* N2 test*) or (clinical* N2 history) or (clinical* N2 histories)) or TX ((physical* N2 assess*) or (physical* N2 exam*) or (physical* N2 test*) or (physical* N2 history) or (physical* N2 histories)) or TX ((Medical* N2 histor*) or (patient* N2 histor*) or Anamnesis) (88,383)

S17 (MH "Patient History Taking+") (8658)

S16 (MH "Physical Examination+") OR (MH "Skin Tests+") (45,744)

S15 (MH "Clinical Assessment Tools+") (66,572)

S14 s9 and s13 (379)

S13 s10 or s11 or s12 (105,090)

S12 TX ((Accident N2 emergency) or (Emergenc* N3 treat*) or (Emergenc* N3 admit*) or (Emergenc* N3 admission*) or (Emergenc* N3 episode*) or (Emergenc* N3 case*) or (Emergenc* N3 patient*) or (Emergenc* N3 department*) or (Emergenc* N3 room*) or (Emergenc* N3 rooms) or (Emergenc* N3 care) or (Emergenc* N3 medic*) or (Emergenc* N3 interven*) or (Emergenc* N3 therap*) or (Emergenc* N3 hospital*) or (Emergenc* N3 service*)) or TX ((Casualty* N3 department*) or (Casualty* N3 admit*) or (Casualty* N3 admission*) or (Casualty* N3 case*) or (Casualty* N3 patient*) or (Casualty* N3 medic*) or (Casualty* N3 interven*) or (Casualty* N3 therap*)) or TX ((postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*)) or TX ((post N1 episod*) or (post N1 admission*) or (post N1 admit*) or (post N1 reaction*) or (post N1 event*) or (post N1 incident*)) (99,683)

S11 (MH "Emergency Medical Services+") (40,158)

S10 (MH "Emergencies") (3245)

S9 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 (30,528)

S8 TX (severe* N2 rash*) or (severity N2 rash*) or (worse* N2 rash*) or (acute* N2 rash*) or (emergenc* N2 rash*) or (urgen* N2 rash*) or (grave* N2 rash*) or (serious* N2 rash*) or (dangerous* N2 rash*) or (life-threat* N2 rash*) or (lifethreat* N2 rash*) or (potentially N3 fatal* N2 rash*) (97)

S7 TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) (9240)

S6 TX ((severe* N3 allerg*) or (severity N3 allerg*) or (worse* N3 allerg*) or (acute* N3 allerg*) or (emergenc* N3 allerg*) or (urgen* N3 allerg*) or (grave* N3 allerg*) or (serious* N3 allerg*)

or (dangerous* N3 allerg*) or (life-threat* N3 allerg*) or (lifethreat* N3 allerg*) or (potentially N3 fatal* N3 allerg*)) or TX ((severe* N3 hypersensiti*) or (severity N3 hypersensiti*) or (worse* N3 hypersensiti*) or (acute* N3 hypersensiti*) or (emergenc* N3 hypersensiti*) or (urgen* N3 hypersensiti*) or (grave* N3 hypersensiti*) or (serious* N3 hypersensiti*) or (dangerous* N3 hypersensiti*) or (life-threat* N3 hypersensiti*) or (lifethreat* N3 hypersensiti*) or (potentially N3 fatal* N3 hypersensiti*)) or TX ((severe* N3 hyper-sensiti*) or (severity N3 hyper-sensiti*) or (worse* N3 hyper-sensiti*) or (acute* N3 hyper-sensiti*) or (emergenc* N3 hyper-sensiti*) or (urgen* N3 hyper-sensiti*) or (grave* N3 hyper-sensiti*) or (serious* N3 hyper-sensiti*) or (dangerous* N3 hyper-sensiti*) or (life-threat* N3 hyper-sensiti*) or (lifethreat* N3 hyper-sensiti*) or (potentially N3 fatal* N3 hyper-sensiti*)) (711)

S5 TI (Anaphyla* or pseudoanaphyla*) or AB (Anaphyla* or pseudoanaphyla*) (1234)

S4 (MH "Latex Hypersensitivity") (1229)

S3 (MH "Food Hypersensitivity+") (1992)

S2 (MH "Drug Hypersensitivity") (1362)

S1 (MH "Hypersensitivity, Immediate+") (20,402)

What are the effects of providing adrenaline auto-injectors, including by whom? (Adrenaline auto-injectors search.)

The auto-injectors search was conducted between February and March 2011.

Medline (OvidSP): 1948 to week 3 February 2011

Searched 24 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (84,731)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15,506)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24,636)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (4381)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (2281)
6. or/1-5 (107,806)
7. ((IM or Intramuscul$ or Intra-muscul$ or inject$) adj3 (Epinephrine or adrenaline)).ti,ab,ot,hw. (1726)
8. (auto-inject$ or autoinject$).ti,ab,ot,hw. (386)
9. (epipen$ or epi-pen$ or anapen$ or ana-pen$ or twinject$ or twin-ject$ or jext$).ti,ab,ot,hw. (94)
10. ((self-medicat$ or selfmedicat$ or selfadminister$ or self-administer$ or selfinject$ or self-inject$) adj3 (Epinephrine or adrenaline)).ti,ab,ot,hw. (99)
11. or/7-10 (2109)
12. 6 and 11 (342)
13. animals/ not (animals/ and humans/) (3,452,597)
14. 12 not 13 (333)

Medline In-Process Citations (OvidSP): up to 23 February 2011
Medline Daily Update (OvidSP): up to 23 February 2011

Searched 24 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (23)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (8)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (553)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (168)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (88)
6. or/1-5 (766)
7. ((IM or Intramuscul$ or Intra-muscul$ or inject$) adj3 (Epinephrine or adrenaline)).ti,ab,ot,hw. (58)
8. (auto-inject$ or autoinject$).ti,ab,ot,hw. (23)
9. (epipen$ or epi-pen$ or anapen$ or ana-pen$ or twinject$ or twin-ject$ or jext$).ti,ab,ot,hw. (6)
10. ((self-medicat$ or selfmedicat$ or selfadminister$ or self-administer$ or selfinject$ or self-inject$) adj3 (Epinephrine or adrenaline)).ti,ab,ot,hw. (5)
11. or/7-10 (77)
12. 6 and 11 (16)
13. animals/ not (animals/ and humans/) (1025)
14. 12 not 13 (16)

EMBASE (OvidSP): 1980 to week 10 2011

Searched 16 March 2011

1. Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88,290)
2. Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18,423)
3. Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32,909)
4. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (39,414)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (5959)
6. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (3063)
7. or/1-6 (137,588)
8. animal/ or animal experiment/ (3,059,048)
9. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,688,188)
10. or/8-9 (4,688,188)
11. exp human/ or human experiment/ (12,277,839)
12. 10 not (10 and 11) (3,764,868)
13. 7 not 12 (123,461)

14. intramuscular drug administration/ (54,836)
15. adrenalin/ (75,165)
16. 14 and 15 (786)
17. adrenalin/im [Intramuscular Drug Administration] (729)
18. ((IM or Intramuscul$ or Intra-muscul$ or inject$) adj3 (Epinephrine or adrenaline)).mp. (2002)
19. (auto-inject$ or autoinject$).mp. (595)
20. (epipen$ or epi-pen$ or anapen$ or ana-pen$ or twinject$ or twin-ject$ or jext$).mp. (427)
21. ((self-medicat$ or selfmedicat$ or selfadminister$ or self-administer$ or selfinject$ or self-inject$) adj3 (Epinephrine or adrenaline)).mp. (160)
22. or/16-21 (4091)
23. 13 and 22 (1340)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 2: 2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1: 2011
http://cochranelibrary.com/

Searched 16 March 2011

1. MeSH descriptor Hypersensitivity, this term only (525)
2. MeSH descriptor Anaphylaxis, this term only (142)
3. MeSH descriptor Asthma, Aspirin-Induced explode all trees (0)
4. MeSH descriptor Drug Hypersensitivity, this term only (403)
5. MeSH descriptor Drug Eruptions explode all trees (354)
6. MeSH descriptor Eosinophilic Esophagitis, this term only (0)
7. MeSH descriptor Hypersensitivity, Immediate, this term only (382)
8. MeSH descriptor Food Hypersensitivity, this term only (381)
9. MeSH descriptor Alveolitis, Extrinsic Allergic, this term only (11)
10. MeSH descriptor Latex Hypersensitivity, this term only (28)
11. MeSH descriptor Aspergillosis, Allergic Bronchopulmonary, this term only (11)
12. (anaphyla* OR pseudoanaphyla*):ti,ab,kw (533)
13. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near3 (allerg* or hypersensiti* or hypersensiti*)):ti,ab,kw (409)
14. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near2 (systemic* or allerg* or skin* or dermatolog* or cutaneous*) near2 (reaction* or effect* or event* or rash*)):ti,ab,kw (107)
15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (2811)
16. ((IM or Intramuscul* or Intra-muscul* or inject*) near3 (Epinephrine or adrenaline)):ti,ab,kw (302)
17. (auto-inject* or autoinject*):ti,ab,kw (38)
18. (epipen* or epi-pen* or anapen* or ana-pen* or twinject* or twin-ject* or jext*):ti,ab,kw (8)
19. ((self-medicat* or selfmedicat* or selfadminister* or self-administer* or selfinject* or self-inject*) near3 (Epinephrine or adrenaline)):ti,ab,kw (3)
20. (#16 OR #17 OR #18 OR #19) (341)
21. (#15 AND #20) (18)

The CDSR search retrieved two records.

The CENTRAL search retrieved 15 records.

Database of Abstracts of Reviews of Effects (DARE) (Internet): 2000 to 16 March 2011
Health Technology Assessment (HTA) (Internet): 2000 to 16 March 2011
NHS Economic Evaluation Database (NHS EED) (Internet): 2000 to 16 March 2011
www.crd.york.ac.uk/crdweb/

Searched 16 March 2011

1. MeSH Hypersensitivity (51)
2. MeSH Drug hypersensitivity (29)
3. MeSH Hypersensitivity, immediate (7)
4. MeSH Anaphylaxis (17)
5. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
6. MeSH food hypersensitivity (14)
7. MeSH alveolitis, extrinsic allergic (0)
8. MeSH aspergillosis, allergic bronchopulmonary (0)
9. MeSH latex hypersensitivity (5)
10. Anaphyla* OR pseudoanaphyla* (80)
11. (severe* NEAR allerg*) OR (severity NEAR allerg*) OR (worse* NEAR allerg*) OR (acute* NEAR allerg*) (117)
12. (emergenc* NEAR allerg*) OR (urgen* NEAR allerg*) OR (grave* NEAR allerg*) OR (serious* NEAR allerg*) (50)
13. (dangerous* NEAR allerg*) OR (life-threat* NEAR allerg*) OR (lifethreat* NEAR allerg*) OR (potentially AND fatal* NEAR allerg*) (12)
14. (severe* NEAR Hypersensiti*) OR (severity NEAR Hypersensiti*) OR (worse* NEAR Hypersensiti*) OR (acute* NEAR Hypersensiti*) (29)
15. (emergenc* NEAR Hypersensiti*) OR (urgen* NEAR Hypersensiti*) OR (grave* NEAR Hypersensiti*) OR (serious* NEAR Hypersensiti*) (11)
16. (dangerous* NEAR Hypersensiti*) OR (life-threat* NEAR Hypersensiti*) OR (lifethreat* NEAR Hypersensiti*) OR (potentially AND fatal* NEAR Hypersensiti*) (5)
17. (severe* NEAR Hyper-sensiti*) OR (severity NEAR Hyper-sensiti*) OR (worse* NEAR Hyper-sensiti*) OR (acute* NEAR Hyper-sensiti*) (29)
18. (emergenc* NEAR Hyper-sensiti*) OR (urgen* NEAR Hyper-sensiti*) OR (grave* NEAR Hyper-sensiti*) OR (serious* NEAR Hyper-sensiti*) (11)
19. (dangerous* NEAR Hyper-sensiti*) OR (life-threat* NEAR Hyper-sensiti*) OR (lifethreat* NEAR Hyper-sensiti*) OR (potentially AND fatal* NEAR Hyper-sensiti*) (5)
20. (severe* NEAR Systemic*) OR (severity NEAR Systemic*) OR (worse* NEAR Systemic*) OR (acute* NEAR Systemic*) (180)
21. (emergenc* NEAR Systemic*) OR (urgen* NEAR Systemic*) OR (grave* NEAR Systemic*) OR (serious* NEAR Systemic*) (41)
22. (dangerous* NEAR Systemic*) OR (life-threat* NEAR Systemic*) OR (lifethreat* NEAR Systemic*) OR (potentially AND fatal* NEAR Systemic*) (18)
23. (dangerous* NEAR Skin) OR (life-threat* NEAR Skin) OR (lifethreat* NEAR Skin) OR (potentially AND fatal* NEAR Skin) (14)
24. (severe* NEAR Skin) OR (severity NEAR Skin) OR (worse* NEAR Skin) OR (acute* NEAR Skin) (175)
25. (emergenc* NEAR Skin) OR (urgen* NEAR Skin) OR (grave* NEAR Skin) OR (serious* NEAR Skin) (85)
26. (severe* NEAR Dermatolog*) OR (severity NEAR Dermatolog*) OR (worse* NEAR Dermatolog*) OR (acute* NEAR Dermatolog*) (41)
27. (emergenc* NEAR Dermatolog*) OR (urgen* NEAR Dermatolog*) OR (grave* NEAR Dermatolog*) OR (serious* NEAR Dermatolog*) (7)
28. (dangerous* NEAR Dermatolog*) OR (life-threat* NEAR Dermatolog*) OR (lifethreat* NEAR Dermatolog*) OR (potentially AND fatal* NEAR Dermatolog*) (0)

29. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (521)
30. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (808)
31. (auto-inject* OR autoinject*) (3)
32. (epipen* OR epi-pen* OR anapen* OR ana-pen* OR twinject* OR twin-ject* OR jext*) (7)
33. (self-medicat* NEAR Epinephrine) OR (selfmedicat* NEAR Epinephrine) OR (selfadminister* NEAR Epinephrine) OR (self-administer* NEAR Epinephrine) OR (selfinject* EAR Epinephrine) OR (self-inject* NEAR Epinephrine) (1)
34. (self-medicat* NEAR Adrenaline) OR (selfmedicat* NEAR Adrenaline) OR (selfadminister* NEAR Adrenaline) OR (self-administer* NEAR Adrenaline) OR (selfinject* NEAR Adrenaline) OR (self-inject* NEAR Adrenaline) (0)
35. (IM NEAR adrenaline) OR (Intramuscul* NEAR adrenaline) OR (Intra-muscul* NEAR adrenaline) OR (inject* NEAR adrenaline) (3)
36. (IM NEAR Epinephrine) OR (Intramuscul* NEAR Epinephrine) OR (Intra-muscul* NEAR Epinephrine) OR (inject* NEAR Epinephrine) (13)
37. #31 or #32 or #33 or #34 or #35 or #36 (25)
38. #30 and #37 (5)

The DARE search retrieved three records.

The NHS EED search retrieved two records.

The HTA search retrieved zero records.

Science Citation Index (SCI) (Web of Science): 1970 to 12 February 2011

Searched 14 February 2011

12 259 #6 and #11
Databases = SCI-EXPANDED Timespan = All Years

11 713 #7 or #8 or #9 or #10
Databases = SCI-EXPANDED Timespan = All Years

10 114 TS = ((self-medicat* or selfmedicat* or selfadminister* or self-administer* or selfinject* or self-inject*) SAME (Epinephrine or adrenaline))
Databases = SCI-EXPANDED Timespan = All Years

9 173 TS = (epipen* or epi-pen* or anapen* or ana-pen* or twinject* or twin-ject* or jext*)
Databases = SCI-EXPANDED Timespan = All Years

8 396 TS = (auto-inject* or autoinject*)
Databases = SCI-EXPANDED Timespan = All Years

7 183 TS = ((IM or Intramuscul* or Intra-muscul* or injector*) SAME (Epinephrine or adrenaline))
Databases = SCI-EXPANDED Timespan = All Years

6 23,983 #4 not #5
Databases = SCI-EXPANDED Timespan = All Years

5 >100,000 TS = (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)

Databases = SCI-EXPANDED Timespan = All Years

4 28,875 #1 or #2 or #3
Databases = SCI-EXPANDED Timespan = All Years

3 7739 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (systemic* or allerg* or skin* or dermatolog* or cutaneous*) SAME (reaction* or effect* or event* or rash*))
Databases = SCI-EXPANDED Timespan = All Years

2 8259 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (allerg* or Hypersensiti* or hyper-sensiti*))
Databases = SCI-EXPANDED Timespan = All Years

1 16,857 TS = (Anaphyla* or pseudoanaphyla*)
Databases = SCI-EXPANDED Timespan = All Years

Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost): 1981 to 18 February 2011

Searched 23 February 2011

S14 s9 and s13 Limiters - Exclude MEDLINE records (2)

S13 s10 or s11 or s12 (249)

S12 TX ((Epinephrine N3 self-medicat*) or (Epinephrine N3 selfmedicat*) or (Epinephrine N3 selfadminister*) or (Epinephrine N3 self-administer*) or (Epinephrine N3 selfinject*) or (Epinephrine N3 self-inject*)) or TX ((Adrenaline N3 self-medicat*) or (Adrenaline N3 selfmedicat*) or (Adrenaline N3 selfadminister*) or (Adrenaline N3 self-administer*) or (Adrenaline N3 selfinject*) or (Adrenaline N3 self-inject*)) (41)

S11 TX ((adrenaline N2 Intramuscul*) or (adrenaline N2 Intra-muscul*) or (adrenaline N2 inject*)) or TX ((Epinephrine N2 Intramuscul*) or (Epinephrine N2 Intra-muscul*) or (Epinephrine N2 inject*)) (161)

S10 TX (auto-inject* or autoinject* or epipen* or epi-pen* or anapen* or ana-pen* or twinject* or twin-ject* or jext*) ((119)

S9 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 ((30528)

S8 TX (severe* N2 rash*) or (severity N2 rash*) or (worse* N2 rash*) or (acute* N2 rash*) or (emergenc* N2 rash*) or (urgen* N2 rash*) or (grave* N2 rash*) or (serious* N2 rash*) or (dangerous* N2 rash*) or (life-threat* N2 rash*) or (lifethreat* N2 rash*) or (potentially N3 fatal* N2 rash*) ((97)

S7 TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2

effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) (9240)

S6 TX ((severe* N3 allerg*) or (severity N3 allerg*) or (worse* N3 allerg*) or (acute* N3 allerg*) or (emergenc* N3 allerg*) or (urgen* N3 allerg*) or (grave* N3 allerg*) or (serious* N3 allerg*) or (dangerous* N3 allerg*) or (life-threat* N3 allerg*) or (lifethreat* N3 allerg*) or (potentially N3 fatal* N3 allerg*)) or TX ((severe* N3 hypersensiti*) or (severity N3 hypersensiti*) or (worse* N3 hypersensiti*) or (acute* N3 hypersensiti*) or (emergenc* N3 hypersensiti*) or (urgen* N3 hypersensiti*) or (grave* N3 hypersensiti*) or (serious* N3 hypersensiti*) or (dangerous* N3 hypersensiti*) or (life-threat* N3 hypersensiti*) or (lifethreat* N3 hypersensiti*) or (potentially N3 fatal* N3 hypersensiti*)) or TX ((severe* N3 hyper-sensiti*) or (severity N3 hyper-sensiti*) or (worse* N3 hyper-sensiti*) or (acute* N3 hyper-sensiti*) or (emergenc* N3 hyper-sensiti*) or (urgen* N3 hyper-sensiti*) or (grave* N3 hyper-sensiti*) or (serious* N3 hyper-sensiti*) or (dangerous* N3 hyper-sensiti*) or (life-threat* N3 hyper-sensiti*) or (lifethreat* N3 hyper-sensiti*) or (potentially N3 fatal* N3 hyper-sensiti*)) (711)

S5 TI (Anaphyla* or pseudoanaphyla*) or AB (Anaphyla* or pseudoanaphyla*) ((1234)

S4 (MH "Latex Hypersensitivity") (1229)

S3 (MH "Food Hypersensitivity+") (1992)

S2 (MH "Drug Hypersensitivity") (1362)

S1 (MH "Hypersensitivity, Immediate+") (20,402)

After assessment, when should referral take place? (Specialist referral search.)

The referral search was conducted between February and March 2011.

MEDLINE (OvidSP): 1948 to week 1 March 2011

Searched 16 March 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (84,975)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15,556)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24,706)

4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (4403)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (2290)
6. or/1-5 (108,132)
7. "referral and consultation"/ or gatekeeping/ (44,777)
8. (Refer$ or consultation$ or Gatekeep$ or gatekeep$).ti,ab,ot,hw. (579,743)
9. (Second opinion$ or 2nd opinion$).ti,ab,ot,hw. (1043)
10. (followup$ or follow-up$ or outpatient$ or out-patient$).ti,ab,ot,hw. (799,644)
11. Outpatient Clinics, Hospital/ (13,094)
12. (Allergist$ or aftercare or after-care).ti,ab,ot,hw. (8709)
13. aftercare/ (6002)
14. or/7-14 (1,332,348)
15. 6 and 15 (6587)
16. animals/ not (animals/ and humans/) (3,464,943)
17. 16 not 17 (6367)
18. exp Emergency Treatment/ (81,416)
19. (Accident adj2 emergency).ti,ab,ot,hw. (3508)
20. exp Emergency Medical Services/ (76,776)
21. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or intervene$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (116,473)
22. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or intervene$ or therap$ or patient$)).ti,ab,ot,hw. (829)
23. (Accident adj2 emergency).ti,ab,ot,hw. (3508)
24. Triage$.ti,ab,ot,hw. (9975)
25. First aid$.ti,ab,ot,hw. (8343)
26. (First response$ or first respond$).ti,ab,ot,hw. (1567)
27. (Medical adj2 urgen$).ti,ab,ot,hw. (431)
28. Emergencies/ (31,418)
29. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (380)
30. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (545)
31. or/19-31 (216,773)
32. 18 and 32 (237)

Medline In-Process Citations (OvidSP): up to 15 March 2011
Medline Daily Update (OvidSP): up to 15 March 2011

Searched 16 March 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (62)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (20)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (586)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (181)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (99)

6. or/1-5 (855)
7. "referral and consultation"/ or gatekeeping/ (51)
8. (Refer$ or consultation$ or Gatekeep$ or gatekeep$).ti,ab,ot,hw. (26,867)
9. (Second opinion$ or 2nd opinion$).ti,ab,ot,hw. (47)
10. (followup$ or follow-up$ or outpatient$ or out-patient$).ti,ab,ot,hw. (22,520)
11. Outpatient Clinics, Hospital/ (4)
12. (Allergist$ or aftercare or after-care).ti,ab,ot,hw. (111)
13. aftercare/ (2)
14. (Allerg$ clinic$ or Specialist clinic$).ti,ab,ot,hw. (78)
15. or/7-14 (47,842)
16. 6 and 15 (72)
17. animals/ not (animals/ and humans/) (3207)
18. 16 not 17 (72)
19. exp Emergency Treatment/ (92)
20. (Accident adj2 emergency).ti,ab,ot,hw. (70)
21. exp Emergency Medical Services/ (139)
22. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or intervene$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (4363)
23. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or intervene$ or therap$ or patient$)).ti,ab,ot,hw. (19)
24. (Accident adj2 emergency).ti,ab,ot,hw. (70)
25. Triage$.ti,ab,ot,hw. (415)
26. First aid$.ti,ab,ot,hw. (115)
27. (First response$ or first respond$).ti,ab,ot,hw. (85)
28. (Medical adj2 urgen$).ti,ab,ot,hw. (27)
29. Emergencies/ (9)
30. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (23)
31. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (34)
32. or/19-31 (4971)
33. 18 and 32 (3)

EMBASE (OvidSP): 1980 to week 10 2011

Searched 17 March 2011

1. Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88,290)
2. Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18,423)
3. Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32,909)
4. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (39,414)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (5959)
6. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ab,ot,hw. (3064)
7. or/1-6 (137,588)
8. Outpatient-Department/ or Patient Referral/ or exp Consultation/ or exp Aftercare/ or Outpatient/ (647,761)
9. (Second opinion$ or 2nd opinion$).mp. (1321)

10. (Refer$ or consultation$ or Gatekeep$ or gatekeep$).mp. (587,999)
11. (followup$ or follow-up$ or outpatient$ or out-patient$).mp. (906,230)
12. (Allergist$ or aftercare or after-care).mp. (8120)
13. (Allerg$ clinic$ or Specialist clinic$).mp. (1752)
14. or/8-13 (1,441,363)
15. emergency treatment/ or evidence based emergency medicine/ or first aid/ or pediatric advanced life support/ (21,042)
16. emergency care/ or EMERGENCY/ or Emergency-Medicine/ or Emergency-Health-Service/ (97,139)
17. Emergency-Patient/ or Emergency-Ward/ (32,763)
18. (Accident adj2 emergency).mp. (4303)
19. (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or interven$ or therap$ or hospital$ or service$)).mp. (168,221)
20. (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or interven$ or therap$ or patient$)).mp. (958)
21. (Triage$ or First aid$ or First response$ or first respond$).mp. (20,469)
22. (Medical adj2 urgen$).mp. (561)
23. (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).mp. (431)
24. (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).mp. (812)
25. or/15-24 (193,229)
26. 7 and 15 and 25 (553)
27. animal/ or animal experiment/ (3,059,048)
28. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,688,188)
29. 27 or 28 (4,688,188)
30. exp human/ or human experiment/ (12,277,839)
31. 29 not (29 and 30) (3,764,868)
32. 26 not 31 (546)

Cochrane Database of Systematic Reviews (CDSR) (Internet): Issue 3: 2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet): Issue 1: 2011
http://cochranelibrary.com/

Searched 17 March 2011

1. MeSH descriptor Hypersensitivity, this term only (525)
2. MeSH descriptor Anaphylaxis, this term only (142)
3. MeSH descriptor Asthma, Aspirin-Induced explode all trees (0)
4. MeSH descriptor Drug Hypersensitivity, this term only (403)
5. MeSH descriptor Drug Eruptions explode all trees (354)
6. MeSH descriptor Eosinophilic Esophagitis, this term only (0)
7. MeSH descriptor Hypersensitivity, Immediate, this term only (382)
8. MeSH descriptor Food Hypersensitivity, this term only (381)
9. MeSH descriptor Alveolitis, Extrinsic Allergic, this term only (11)
10. MeSH descriptor Latex Hypersensitivity, this term only (28)
11. MeSH descriptor Aspergillosis, Allergic Bronchopulmonary, this term only (11)
12. (anaphyla* OR pseudoanaphyla*):ti,ab,kw (533)
13. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near3 (allerg* or hypersensiti* or hyper-sensiti*)):ti,ab,kw (409)
14. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near2 (systemic* or allerg* or skin* or dermatolog* or cutaneous*) near2 (reaction* or effect* or event* or rash*)):ti,ab,kw (107)

15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (2811)
16. MeSH descriptor Referral and Consultation, this term only (1374)
17. MeSH descriptor Gatekeeping, this term only (15)
18. MeSH descriptor Outpatient Clinics, Hospital, this term only (601)
19. MeSH descriptor Aftercare, this term only (402)
20. (Refer* or consultation* or Gate-keep* or gatekeep*):ti,ab,kw (37,266)
21. ((Second near2 opinion*) or (2nd near2 opinion*)):ti,ab,kw 37)
22. (followup* or follow-up* or outpatient* or out-patient*):ti,ab,kw (88,074)
23. (Allergist* or aftercare or after-care):ti,ab,kw (642)
24. ((Allerg* near2 clinic*) or (Specialist near2 clinic*)):ti,ab,kw (378)
25. (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) (118,191)
26. MeSH descriptor Emergency Treatment explode all trees (3358)
27. MeSH descriptor Emergency Medical Services explode all trees (2535)
28. MeSH descriptor Emergencies, this term only (609)
29. (Accident near2 emergency):ti,ab,kw (203)
30. (Emergenc* near3 (treat* or admit* or admission* or episode* or case* or patient* or department* or room* or rooms or care or medic* or interven* or therap* or hospital* or service*)):ti,ab,kw (5783)
31. (Casualty near2 (department* or admit* or admission* or patient* or case* or care or medicat* or interven* or therap* or patient*)):ti,ab,kw (35)
32. (Accident near2 emergency):ti,ab,kw (203)
33. Triage*:ti,ab,kw (435)
34. (First near1 aid*):ti,ab,kw (122)
35. (First near1 respons*):ti,ab,kw (247)
36. (First near1 respond*):ti,ab,kw (111)
37. (Medical near2 urgen*):ti,ab,kw (12)
38. (postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*):ti,ab,kw (39)
39. (post near (episod* or admission* or admit* or reaction* or event* or incident*)):ti,ab,kw (520)
40. (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39) (10,192)
41. (#15 AND #25 AND #40) (4)

The CDSR search retrieved zero records.

The CENTRAL search retrieved two records.

Database of Abstracts of Reviews of Effects (DARE) (Internet): 2000 to 17 February 2011
Health Technology Assessment (HTA) (Internet): 2000 to 17 February 2011
NHS Economic Evaluation Database (NHS EED) (Internet): 2000 to 17 February 2011
www.crd.york.ac.uk/crdweb/

Searched 17 March 2011

1. MeSH Hypersensitivity (51)
2. MeSH Drug hypersensitivity (29)
3. MeSH Hypersensitivity, immediate (7)
4. MeSH Anaphylaxis (17)
5. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
6. MeSH food hypersensitivity (14)
7. MeSH alveolitis, extrinsic allergic (0)

8. MeSH aspergillosis, allergic bronchopulmonary (0)
9. MeSH latex hypersensitivity (5))
10. Anaphyla* OR pseudoanaphyla* (80)
11. (severe* NEAR allerg*) OR (severity NEAR allerg*) OR (worse* NEAR allerg*) OR (acute* NEAR allerg*) (117)
12. (emergenc* NEAR allerg*) OR (urgen* NEAR allerg*) OR (grave* NEAR allerg*) OR (serious* NEAR allerg*) (50)
13. (dangerous* NEAR allerg*) OR (life-threat* NEAR allerg*) OR (lifethreat* NEAR allerg*) OR (potentially AND fatal* NEAR allerg*) (12)
14. (severe* NEAR Hypersensiti*) OR (severity NEAR Hypersensiti*) OR (worse* NEAR Hypersensiti*) OR (acute* NEAR Hypersensiti*) (29)
15. (emergenc* NEAR Hypersensiti*) OR (urgen* NEAR Hypersensiti*) OR (grave* NEAR Hypersensiti*) OR (serious* NEAR Hypersensiti*) (11)
16. (dangerous* NEAR Hypersensiti*) OR (life-threat* NEAR Hypersensiti*) OR (lifethreat* NEAR Hypersensiti*) OR (potentially AND fatal* NEAR Hypersensiti*) (5)
17. (severe* NEAR Hyper-sensiti*) OR (severity NEAR Hyper-sensiti*) OR (worse* NEAR Hyper-sensiti*) OR (acute* NEAR Hyper-sensiti*) (29)
18. (emergenc* NEAR Hyper-sensiti*) OR (urgen* NEAR Hyper-sensiti*) OR (grave* NEAR Hyper-sensiti*) OR (serious* NEAR Hyper-sensiti*) (11)
19. (dangerous* NEAR Hyper-sensiti*) OR (life-threat* NEAR Hyper-sensiti*) OR (lifethreat* NEAR Hyper-sensiti*) OR (potentially AND fatal* NEAR Hyper-sensiti*) (5)
20. (severe* NEAR Systemic*) OR (severity NEAR Systemic*) OR (worse* NEAR Systemic*) OR (acute* NEAR Systemic*) (180)
21. (emergenc* NEAR Systemic*) OR (urgen* NEAR Systemic*) OR (grave* NEAR Systemic*) OR (serious* NEAR Systemic*) (41)
22. (dangerous* NEAR Systemic*) OR (life-threat* NEAR Systemic*) OR (lifethreat* NEAR Systemic*) OR (potentially AND fatal* NEAR Systemic*) (18)
23. (dangerous* NEAR Skin) OR (life-threat* NEAR Skin) OR (lifethreat* NEAR Skin) OR (potentially AND fatal* NEAR Skin) (14)
24. (severe* NEAR Skin) OR (severity NEAR Skin) OR (worse* NEAR Skin) OR (acute* NEAR Skin) (175)
25. (emergenc* NEAR Skin) OR (urgen* NEAR Skin) OR (grave* NEAR Skin) OR (serious* NEAR Skin) (85)
26. (severe* NEAR Dermatolog*) OR (severity NEAR Dermatolog*) OR (worse* NEAR Dermatolog*) OR (acute* NEAR Dermatolog*) (41)
27. (emergenc* NEAR Dermatolog*) OR (urgen* NEAR Dermatolog*) OR (grave* NEAR Dermatolog*) OR (serious* NEAR Dermatolog*) (7)
28. (dangerous* NEAR Dermatolog*) OR (life-threat* NEAR Dermatolog*) OR (lifethreat* NEAR Dermatolog*) OR (potentially AND fatal* NEAR Dermatolog*) (0)
29. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (521)
30. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (808)
31. Refer* OR consultation* OR Gatekeep* OR gate-keep* (14,313)
32. (Second NEAR opinion*) OR (2nd NEAR opinion*) (70)
33. (followup* OR follow-up* OR outpatient* OR out-patient*) (13,004)
34. (Allergist* OR aftercare OR after-care) (56)
35. ((Allerg* NEAR clinic*) OR (Specialist NEAR clinic*)) (559)
36. #31 or #32 or #33 or #34 or #35 (20,112)
37. #30 and #36 (524)
38. (Accident NEAR emergency) (127)
39. (Emergenc* NEAR treat*) OR (Emergenc* NEAR admit*) OR (Emergenc* NEAR admission*) OR (Emergenc* NEAR episode*) (787)
40. (Emergenc* NEAR case*) OR (Emergenc* NEAR patient*) OR (Emergenc* NEAR department*) OR (Emergenc* NEAR room*) (1593)
41. (Emergenc* NEAR rooms) OR (Emergenc* NEAR care) OR (Emergenc* NEAR medic*) (1277)

42. (Emergenc* NEAR interven*) OR (Emergenc* NEAR therap*) OR (Emergenc* NEAR hospital*) OR (Emergenc* NEAR service*) (1328)
43. (Casualty NEAR department*) OR (casualty NEAR admit*) OR (casualty NEAR admission*) OR (casualty NEAR patient*) (10)
44. (casualty NEAR case*) OR (casualty NEAR care) OR (casualty NEAR medicat*) (7)
45. (casualty NEAR interven*) OR (casualty NEAR therap*) OR (casualty NEAR patient*) (7)
46. (triage* OR (First NEAR aid*) OR (First NEAR respons*) OR (First NEAR respond*) OR (Medical NEAR urgen*)) (643)
47. (postepisod* OR postadmission* OR postadmit* OR postreaction* OR postevent* OR postincident*) (2)
48. (post NEAR episod*) OR (post NEAR admission*) OR (post NEAR admit*) OR (post NEAR reaction*) (235)
49. (post NEAR event*) OR (post NEAR incident*) (365)
50. #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 (3051)
51. #37 and #50 (93)

The DARE search retrieved 42 records.

The NHS EED search retrieved 49 records.

The HTA search retrieved two records.

Science Citation Index (SCI) (Web of Science): 1970 to 12 February 2011

Searched 14 February 2011

21 1033 #6 and #13 and #20
Databases = SCI-EXPANDED Timespan = All Years

20 >100,000 #14 or #15 or #16 or #17 or #18 or #19
Databases = SCI-EXPANDED Timespan = All Years

19 28,865 TS = (Allerg* clinic* or Specialist clinic*)
Databases = SCI-EXPANDED Timespan = All Years

18 33,283 TS = (Aftercare or outpatient* clinic*)
Databases = SCI-EXPANDED Timespan = All Years

17 >100,000 TS = (Allergist* or aftercare or after-care)
Databases = SCI-EXPANDED Timespan = All Years

16 >100,000 TS = (followup* or follow-up* or outpatient* or out-patient*)
Databases = SCI-EXPANDED Timespan = All Years

15 2720 TS = (Second opinion* or 2nd opinion*)
Databases = SCI-EXPANDED Timespan = All Years

14 >100,000 TS = (Refer* or consultation* or Gatekeep* or gatekeep*)
Databases = SCI-EXPANDED Timespan = All Years

13 >100,000 #7 or #8 or #9 or #10 or #11 or #12
Databases = SCI-EXPANDED Timespan = All Years

12 71,359 TS = (Emergenc* SAME (treat* or admit* or admission* or episode* or case* or patient* or department* or room* or rooms or care or medic* or interven* or therap* or hospital* or service*))
Databases = SCI-EXPANDED Timespan = All Years

11 682 TS = (Casualty SAME (department* or admit* or admission* or patient* or case* or care or medicat* or interven* or therap* or patient*))
Databases = SCI-EXPANDED Timespan = All Years

10 3039 TS = ((Triage*or First aid*) or (Accident SAME emergency))
Databases = SCI-EXPANDED Timespan = All Years

9 >100,000 TS = ((Medical SAME urgen*) or (First response* or first respond*))
Databases = SCI-EXPANDED Timespan = All Years

8 372 TS = (postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*)
Databases = SCI-EXPANDED Timespan = All Years

7 13,113 TS = (post SAME (episod* or admission* or admit* or reaction* or event* or incident*))
Databases = SCI-EXPANDED Timespan = All Years

6 23,983 #4 not #5
Databases = SCI-EXPANDED Timespan = All Years

5 >100,000 TS = (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
Databases = SCI-EXPANDED Timespan = All Years

4 28,875 #1 or #2 or #3
Databases = SCI-EXPANDED Timespan = All Years

3 7739 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (systemic* or allerg* or skin* or dermatolog* or cutaneous*) SAME (reaction* or effect* or event* or rash*))
Databases = SCI-EXPANDED Timespan = All Years

2 8259 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (allerg* or Hypersensiti* or hyper-sensiti*))
Databases = SCI-EXPANDED Timespan = All Years

1 16,857 TS = (Anaphyla* or pseudoanaphyla*)
Databases = SCI-EXPANDED Timespan = All Years

Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost): 1981 to 18 February 2011

Searched 23 February 2011
S21 s13 and s20 Limiters - Exclude MEDLINE records (23)

S20 s14 or s15 or s16 or s17 or s18 or s19 (579,982)

S19 TX ((Refer* or consultation* or Gatekeep* or gate-keep* or Allergist* or aftercare or after-care)) or TX ((Second N1 opinion*) or (2nd N1 opinion*) or (followup* or follow-up* or outpatient* or out-patient*)) or TX ((Allerg* N2 clinic*) or (Specialist N2 clinic*)) (579,982)

S18 (MH "After Care") (4003)

S17 (MH "Outpatient Service") (2648)

S16 (MH "Outpatients") (25,019)

S15 (MH "Gatekeeping") (187)

S14 (MH "Referral and Consultation+") (12,876)

S13 s9 and s12 (379)

S12 s10 or s11 (105,090)

S11 TX ((Accident N2 emergency) or (Emergenc* N3 treat*) or (Emergenc* N3 admit*) or (Emergenc* N3 admission*) or (Emergenc* N3 episode*) or (Emergenc* N3 case*) or (Emergenc* N3 patient*) or (Emergenc* N3 department*) or (Emergenc* N3 room*) or (Emergenc* N3 rooms) or (Emergenc* N3 care) or (Emergenc* N3 medic*) or (Emergenc* N3 interven*) or (Emergenc* N3 therap*) or (Emergenc* N3 hospital*) or (Emergenc* N3 service*)) or TX ((Casualty* N3 department*) or (Casualty* N3 admit*) or (Casualty* N3 admission*) or (Casualty* N3 case*) or (Casualty* N3 patient*) or (Casualty* N3 medic*) or (Casualty* N3 interven*) or (Casualty* N3 therap*)) or TX ((postepisod* or postadmission* or postadmit* or postreaction* or postevent* or postincident*)) or TX ((post N1 episod*) or (post N1 admission*) or (post N1 admit*) or (post N1 reaction*) or (post N1 event*) or (post N1 incident*)) (99,683)

S10 (MH "Emergencies") or (MH "Emergency Medical Services+") (42,909)

S9 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 (30,528)

S8 TX (severe* N2 rash*) or (severity N2 rash*) or (worse* N2 rash*) or (acute* N2 rash*) or (emergenc* N2 rash*) or (urgen* N2 rash*) or (grave* N2 rash*) or (serious* N2 rash*) or (dangerous* N2 rash*) or (life-threat* N2 rash*) or (lifethreat* N2 rash*) or (potentially N3 fatal* N2 rash*) (97)

S7 TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat*

N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) (9240)

S6 TX ((severe* N3 allerg*) or (severity N3 allerg*) or (worse* N3 allerg*) or (acute* N3 allerg*) or (emergenc* N3 allerg*) or (urgen* N3 allerg*) or (grave* N3 allerg*) or (serious* N3 allerg*) or (dangerous* N3 allerg*) or (life-threat* N3 allerg*) or (lifethreat* N3 allerg*) or (potentially N3 fatal* N3 allerg*)) or TX ((severe* N3 hypersensiti*) or (severity N3 hypersensiti*) or (worse* N3 hypersensiti*) or (acute* N3 hypersensiti*) or (emergenc* N3 hypersensiti*) or (urgen* N3 hypersensiti*) or (grave* N3 hypersensiti*) or (serious* N3 hypersensiti*) or (dangerous* N3 hypersensiti*) or (life-threat* N3 hypersensiti*) or (lifethreat* N3 hypersensiti*) or (potentially N3 fatal* N3 hypersensiti*)) or TX ((severe* N3 hyper-sensiti*) or (severity N3 hyper-sensiti*) or (worse* N3 hyper-sensiti*) or (acute* N3 hyper-sensiti*) or (emergenc* N3 hyper-sensiti*) or (urgen* N3 hyper-sensiti*) or (grave* N3 hyper-sensiti*) or (serious* N3 hyper-sensiti*) or (dangerous* N3 hyper-sensiti*) or (life-threat* N3 hyper-sensiti*) or (lifethreat* N3 hyper-sensiti*) or (potentially N3 fatal* N3 hyper-sensiti*)) (711)

S5 TI (Anaphyla* or pseudoanaphyla*) or AB (Anaphyla* or pseudoanaphyla*) (1234)

S4 (MH "Latex Hypersensitivity") (1229)

S3 (MH "Food Hypersensitivity+") (1992)

S2 (MH "Drug Hypersensitivity") (1362)

S1 (MH "Hypersensitivity, Immediate+") (20,402)

In adults, young people and children who receive emergency treatment for suspected anaphylaxis, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration? (Risk of recurrence search.)

The risk of recurrence search was conducted in February 2011.

Medline (OvidSP): 1948 to week 1 February 2011

Searched 11 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83,258)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15,288)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24,149)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (4316)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (2250)

6. or/1-5 (105,987)
7. Recurrence/ (135,626)
8. (Recrudescen$ or recur$ or repeat$ or re-occur$ or reoccur$ or subsequent$ or repetition$ or repeat$).ti,ab,ot,hw. (1,090,520)
9. (Future adj3 (episode$ or event$ or inciden$ or occur$ or experience$ or attack$ or bout$)).ti,ab,ot,hw. (4426)
10. or/7-9 (1,094,231)
11. risk/ or risk assessment/ or risk factors/ (597,934)
12. (risk or risks or likelihood$).ti,ab,ot,hw. (1,200,489)
13. or/11-12 (1,200,489)
14. 10 and 13 (143,543)
15. 6 and 14 (1168)
16. animals/ not (animals/ and humans/) (3,403,655)
17. 15 not 16 (1130)

Medline In-Process Citations (OvidSP): up to 10 February 2011
Medline Daily Update (OvidSP): up to 10 February 2011

Searched 11 February 2011

1. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (28)
2. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (9)
3. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (572)
4. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (173)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (95)
6. or/1-5 (798)
7. Recurrence/ (66)
8. (Recrudescen$ or recur$ or repeat$ or re-occur$ or reoccur$ or subsequent$ or repetition$ or repeat$).ti,ab,ot,hw. (47,641)
9. (Future adj3 (episode$ or event$ or inciden$ or occur$ or experience$ or attack$ or bout$)).ti,ab,ot,hw. (274)
10. or/7-9 (47,873)
11. risk/ or risk assessment/ or risk factors/ (737)
12. (risk or risks or likelihood$).ti,ab,ot,hw. (46,261)
13. or/11-12 (46,261)
14. 10 and 13 (5026)
15. 6 and 14 (10)
16. animals/not (animals/ and humans/) (1531)
17. 15 not 16 (10)

Embase (OvidSP): 1980 to week 6 2011

Searched 14 February 2011

1. Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (87,798)
2. Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18,305)

3. Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32,758)
4. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (39,238)
5. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (5910)
6. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (3040)
7. or/1-6 (136,815)
8. Recurrent-Disease/ (106,106)
9. (Recrudescen$ or recur$ or repeat$ or re-occur$ or reoccur$ or subsequent$ or repetition$ or repeat$).ti,ab,ot,hw. (1,256,741)
10. (Future adj3 (episode$ or event$ or inciden$ or occur$ or experience$ or attack$ or bout$)).ti,ab,ot,hw. (5783)
11. or/8-10 (1,261,628)
12. risk/ or attributable risk/ or behavioral risk factor surveillance system/ or genetic risk/ or high risk behavior/ or high risk infant/ or high risk patient/ or high risk population/ or high risk pregnancy/ or population risk/ or risk assessment/ or risk factor/ or risk management/ or risk reduction/ (8,646,42)
13. (risk or risks or likelihood$).ti,ab,ot,hw. (1,580,892)
14. or/12-13 (1,580,892)
15. 11 and 14 (185,931)
16. Recurrence-Risk/ (20,568)
17. 15 or 16 (185,931)
18. 7 and 17 (2354)
19. animal/ or animal experiment/ (3,045,231)
20. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,666,017)
21. or/19-20 (4,666,017)
22. exp human/ or human experiment/ (12,216,815)
23. 21 not (21 and 22) (3,748,300)
24. 18 not 23 (2304)

Cochrane Database of Systematic Reviews (CDSR) (Internet): Issue 1: 2011
Cochrane Central Register of Controlled Trials (CENTRAL) (Internet): Issue 1: 2011
http://cochranelibrary.com/

Searched 17 February 2011

1. MeSH descriptor Hypersensitivity, this term only (525)
2. MeSH descriptor Anaphylaxis, this term only (142)
3. MeSH descriptor Asthma, Aspirin-Induced explode all trees (0)
4. MeSH descriptor Drug Hypersensitivity, this term only (403)
5. MeSH descriptor Drug Eruptions explode all trees (353)
6. MeSH descriptor Eosinophilic Esophagitis, this term only (0)
7. MeSH descriptor Hypersensitivity, Immediate, this term only (382)
8. MeSH descriptor Food Hypersensitivity, this term only (381)
9. MeSH descriptor Alveolitis, Extrinsic Allergic, this term only (11)
10. MeSH descriptor Latex Hypersensitivity, this term only (28)
11. MeSH descriptor Aspergillosis, Allergic Bronchopulmonary, this term only (11)
12. (anaphyla* OR pseudoanaphyla*):ti,ab,kw (533)

13. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near3 (allerg* or hypersensiti* or hypersensiti*)):ti,ab,kw (409)
14. ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat or potentially fatal*) near2 (systemic* or allerg* or skin* or dermatolog* or cutaneous*) near2 (reaction* or effect* or event* or rash*)):ti,ab,kw (107)
15. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) (2810)
16. MeSH descriptor Recurrence, this term only (10,438)
17. (recrudescen* OR recur* OR repeat* OR re-occur* OR subsequent* OR repetition* OR repeat*):ti,ab,kw (59,339)
18. (future NEAR (episode* OR event* OR inciden* OR occur* OR experience* OR attack* OR bout*)):ti,ab,kw (299)
19. (#17 OR #17 OR #18) (59,572)
20. MeSH descriptor Risk, this term only (2429)
21. MeSH descriptor Risk Assessment, this term only (5376)
22. MeSH descriptor Risk Factors, this term only (15,176)
23. (risk or risks OR likelihood*):ti,ab,kw (66,166)
24. (#20 OR #21 OR #22 OR #23) (66,166)
25. (#15 AND #19 AND #24) (59)

The CDSR search retrieved two records.

The CENTRAL search retrieved 57 records.

Database of Abstracts of Reviews of Effects (DARE) (Internet): 2000 to 17 February 2011
Health Technology Assessment (HTA) (Internet): 2000 to 17 February 2011
NHS Economic Evaluation Database (NHS EED) (Internet): 2000 to 17 February 2011
www.crd.york.ac.uk/crdweb/

Searched 17 February 2011

1. MeSH Hypersensitivity (51)
2. MeSH drug hypersensitivity (29)
3. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
4. MeSH Hypersensitivity, Immediate (7)
5. MeSH Anaphylaxis (17)
6. asthma, AND aspirin-induced (1)
7. eosinophilic AND esophagitis (3)
8. #1 or #2 or #3 or #4 or #5 or #7 (113)
9. MeSH Food Hypersensitivity (13)
10. MeSH Alveolitis, Extrinsic Allergic (0)
11. MeSH Aspergillosis, Allergic Bronchopulmonary (0)
12. MeSH Latex Hypersensitivity (5)
13. #9 or #10 or #11 or #12 (18)
14. (anaphyla* OR pseudoanaphyla*) (80)
15. severe* NEAR hyper-sensiti* (21)
16. Severity NEAR hyper-sensi* (0)
17. Worse* NEAR hyper-sensi* (1)
18. Acute* NEAR hyper-sensi* (12)
19. Emergenc* NEAR hyper-sensi* (0)
20. Urgen* NEAR hyper-sensi* (2)

21. Grave* NEAR hyper-sensi* (0)
22. Serious* NEAR hyper-sensi* (9)
23. Dangerous* NEAR hyper-sensi* (0)
24. Life-threat* NEAR hyper-sensi* (1)
25. Lifethreat* NEAR hyper-sensi* (0)
26. potentially-fatal* NEAR hyper-sensi* (0)
27. #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 (38)
28. Severity NEAR allerg* (25)
29. Worse* NEAR allerg* (4)
30. Acute* NEAR allerg* (33)
31. Emergenc* NEAR allerg* (19)
32. Urgen* NEAR allerg* (4)
33. Grave* NEAR allerg* (0)
34. Serious* NEAR allerg* (30)
35. Dangerous* NEAR allerg* (2)
36. Life-threat* NEAR allerg* (6)
37. Lifethreat* NEAR allerg* (0)
38. Potentially-fatal* NEAR allerg* (2)
39. severe* NEAR allerg* (68)
40. #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or 38 or #39 (161)
41. Worse* NEAR hypersensiti* (1)
42. Acute* NEAR hypersensiti* (11)
43. Emergenc* NEAR hypersensiti* (0)
44. Urgen* NEAR hypersensiti* (2)
45. Grave* NEAR hypersensiti* (0)
46. Serious* NEAR hypersensiti* (9)
47. Dangerous* NEAR hypersensiti* (0)
48. Lifethreat* NEAR hypersensiti* (0)
49. Potentially-fatal* NEAR hypersensiti* (0)
50. life-threat* NEAR hypersensiti* (1)
51. severe* NEAR hypersensiti* (21)
52. severity NEAR AND hypersensiti* (0)
53. #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 (37)
54. (systemic* NEAR reaction*) OR (allerg* NEAR reaction*) OR (skin* NEAR reaction*) OR (dermatolog* NEAR reaction*) OR (cutaneous* NEAR reaction*) (244)
55. (systemic* NEAR effect*) OR (allerg* NEAR effect*) OR (skin* NEAR effect*) OR (dermatolog* NEAR effect*) OR (cutaneous* NEAR effect*) (1317)
56. (systemic* NEAR event*) OR (allerg* NEAR event*) OR (skin* NEAR event*) OR (dermatolog* NEAR event*) OR (cutaneous* NEAR event*) (241)
57. (systemic* NEAR rash*) OR (allerg* NEAR rash*) OR (skin* NEAR rash*) OR (dermatolog* NEAR rash*) OR (cutaneous* NEAR rash*) (79)
58. #54 or #55 or #56 or #57 (1533)
59. #8 or #13 or #14 or #27 or #40 or #53 or #58 (1734)
60. MeSH Recurrence (946)
61. (recrudescen* OR recur* OR repeat* OR re-occur* OR reoccur* OR subsequent* OR repetition* OR repeat*) (5726)
62. (future NEAR episode*) OR (future NEAR event*) OR (future NEAR inciden*) (318)
63. (future NEAR occur*) OR (future NEAR experience*) OR (future NEAR attack*) OR (future NEAR bout*) (177)
64. #62 OR #63 (470)
65. #60 OR #61 OR #64 (6596)
66. MeSH Risk (490)

67. MeSH Risk assessment (1274)
68. MeSH Risk Factors (2459)
69. #66 or #67 or #68 (3921)
70. (risk OR risks OR likelihood*) (13,669)
71. #69 or #70 (15,477)
72. #65 AND #71 (3369)
73. #59 AND #72 (200)

The DARE search retrieved 129 records.

The NHS EED search retrieved 61 records.

The HTA search retrieved 10 records.

Science Citation Index (SCI) (Web of Science): 1970 to 12 February 2011

Searched 14 February 2011

12 3367 #10 not #11
Databases = SCI-EXPANDED Timespan = All Years

11 >100,000 TS = (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
Databases = SCI-EXPANDED Timespan = All Years

10 3702 #4 and #8
Databases = SCI-EXPANDED Timespan = All Years

9 >100,000 #5 and #7
Databases = SCI-EXPANDED Timespan = All Years

8 >100,000 TS = (risk or risks or likelihood*)
Databases = SCI-EXPANDED Timespan = All Years

7 >100,000 #6 OR #5
Databases = SCI-EXPANDED Timespan = All Years

6 14,633 TS = (Future SAME (episode* or event* or inciden* or occur* or experience* or attack* or bout*))
Databases = SCI-EXPANDED Timespan = All Years

5 >100,000 TS = (Recrudescen* or recur* or repeat* or re-occur* or reoccur* or subsequent* or repetition* or repeat*)
Databases = SCI-EXPANDED Timespan = All Years

4 28,875 #1 or #2 or #3
Databases = SCI-EXPANDED Timespan = All Years

3 7739 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (systemic* or allerg* or skin* or dermatolog* or cutaneous*) SAME (reaction* or effect* or event* or rash*))
Databases = SCI-EXPANDED Timespan = All Years

2 8259 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (allerg* or Hypersensiti* or hyper-sensiti*))
Databases = SCI-EXPANDED Timespan = All Years

1 16,857 TS = (Anaphyla* or pseudoanaphyla*)
Databases = SCI-EXPANDED Timespan = All Years

Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost): 1981 to 18 February 2011

Searched 23 February 2011

S17 s9 and s16 Limiters - Exclude MEDLINE records (196)

S16 s12 and s15 (22,108)

S15 s13 or s14 (250,339)

S14 TX (risk or risks or likelihood*) (250,339)

S13 (MH "Risk Assessment") OR (MH "Risk Factors") (64,318)

S12 s10 or s11 (97,852)

S11 TX (Recrudescen* or recur* or repeat* or re-occur* or reoccur* or subsequent* or repetition* or repeat*) or TX ((Future N3 episode*) or (Future N3 event*) or (Future N3 inciden*) or (Future N3 occur*) or (Future N3 experienc*) or (Future N3 attack*) or (Future N3 bout*)) (97,852)

S10 (MH "Recurrence") (12,583)

S9 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 (30,528)

S8 TX (severe* N2 rash*) or (severity N2 rash*) or (worse* N2 rash*) or (acute* N2 rash*) or (emergenc* N2 rash*) or (urgen* N2 rash*) or (grave* N2 rash*) or (serious* N2 rash*) or (dangerous* N2 rash*) or (life-threat* N2 rash*) or (lifethreat* N2 rash*) or (potentially N3 fatal* N2 rash*) (97)

S7 TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat*

N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) (9240)

S6 TX ((severe* N3 allerg*) or (severity N3 allerg*) or (worse* N3 allerg*) or (acute* N3 allerg*) or (emergenc* N3 allerg*) or (urgen* N3 allerg*) or (grave* N3 allerg*) or (serious* N3 allerg*) or (dangerous* N3 allerg*) or (life-threat* N3 allerg*) or (lifethreat* N3 allerg*) or (potentially N3 fatal* N3 allerg*)) or TX ((severe* N3 hypersensiti*) or (severity N3 hypersensiti*) or (worse* N3 hypersensiti*) or (acute* N3 hypersensiti*) or (emergenc* N3 hypersensiti*) or (urgen* N3 hypersensiti*) or (grave* N3 hypersensiti*) or (serious* N3 hypersensiti*) or (dangerous* N3 hypersensiti*) or (life-threat* N3 hypersensiti*) or (lifethreat* N3 hypersensiti*) or (potentially N3 fatal* N3 hypersensiti*)) or TX ((severe* N3 hyper-sensiti*) or (severity N3 hyper-sensiti*) or (worse* N3 hyper-sensiti*) or (acute* N3 hyper-sensiti*) or (emergenc* N3 hyper-sensiti*) or (urgen* N3 hyper-sensiti*) or (grave* N3 hyper-sensiti*) or (serious* N3 hyper-sensiti*) or (dangerous* N3 hyper-sensiti*) or (life-threat* N3 hyper-sensiti*) or (lifethreat* N3 hyper-sensiti*) or (potentially N3 fatal* N3 hyper-sensiti*)) (711)

S5 TI (Anaphyla* or pseudoanaphyla*) or AB (Anaphyla* or pseudoanaphyla*) (1234)

S4 (MH "Latex Hypersensitivity") ((1229)

S3 (MH "Food Hypersensitivity+") ((1992)

S2 (MH "Drug Hypersensitivity") ((1362)

S1 (MH "Hypersensitivity, Immediate+") ((20,402)

Health economic search

The following sources were searched to identify economic evaluations and quality-of-life data. These searches were conducted between February and March 2011.

MEDLINE (OvidSP): 1948 to week 2 March 2011

Searched 17 March 2011

1. economics/ (25,965)
2. exp "costs and cost analysis"/ (154,360)
3. economics, dental/ (1814)
4. exp "economics, hospital"/ (17,009)
5. economics, medical/ (8379)
6. economics, nursing/ (3839)
7. economics, pharmaceutical/ (2194)
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (327,719)
9. (expenditure$ not energy).ti,ab. (13,900)
10. (value adj1 money).ti,ab. (18)
11. budget$.ti,ab. (14,162)
12. or/1-11 (439,089)
13. ((energy or oxygen) adj cost).ti,ab. (2243)
14. (metabolic adj cost).ti,ab. (578)

15. ((energy or oxygen) adj expenditure).ti,ab. (12,794)
16. or/13-15 (15,012)
17. 12 not 16 (435,668)
18. letter.pt. (707,514)
19. editorial.pt. (270,646)
20. historical article.pt. (271,900)
21. or/18-20 (1,237,508)
22. 17 not 21 (411,802)
23. animals/ not (animals/ and humans/) (3,467,241)
24. 22 not 23 (388,655)
25. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (85,022)
26. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15,572)
27. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24,719)
28. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (4407)
29. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (2291)
30. or/25-29 (108,202)
31. 24 and 30 (1048)

Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 13 January 2011]. Available from: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

Medline In-Process Citations (OvidSP): up to 16 March 2011
Medline Daily Update (OvidSP): up to 16 March 2011

Searched 17 March 2011

1. economics/ (4)
2. exp "costs and cost analysis"/ (74)
3. economics, dental/ (0)
4. exp "economics, hospital"/ (8)
5. economics, medical/ (0)
6. economics, nursing/ (0)
7. economics, pharmaceutical/ (1)
8. (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (21,859)
9. (expenditure$ not energy).ti,ab. (657)
10. (value adj1 money).ti,ab. (2)
11. budget$.ti,ab. (1252)
12. or/1-11 (23,138)
13. ((energy or oxygen) adj cost).ti,ab. (144)
14. (metabolic adj cost).ti,ab. (36)
15. ((energy or oxygen) adj expenditure).ti,ab. (507)
16. or/13-15 (665)
17. 12 not 16 (22,934)
18. letter.pt. (15,937)
19. editorial.pt. (9720)
20. historical article.pt. (115)

21. or/18-20 (25,758)
22. 17 not 21 (22,640)
23. animals/ not (animals/ and humans/) (1312)
24. 22 not 23 (22,627)
25. hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (40)
26. food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (7)
27. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (574)
28. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (176)
29. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (98)
30. or/25-29 (810)
31. 24 and 30 (21)

Based on Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 13 January 2011]. Available from: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

EMBASE (OvidSP): 1980 to week 10 2011

Searched 17 March 2011

1. health-economics/ (29,979)
2. exp economic-evaluation/ (164,685)
3. exp health-care-cost/ (158,213)
4. exp pharmacoeconomics/ (135,242)
5. or/1-4 (379,306)
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (422,362)
7. (expenditure$ not energy).ti,ab. (16,881)
8. (value adj2 money).ti,ab. (884)
9. budget$.ti,ab. (17,911)
10. or/6-9 (440,596)
11. 5 or 10 (666,254)
12. letter.pt. (721,412)
13. editorial.pt. (367,270)
14. note.pt. (436,494)
15. or/12-14 (1,525,176)
16. 11 not 15 (596,935)
17. (metabolic adj cost).ti,ab. (638)
18. ((energy or oxygen) adj cost).ti,ab. (2507)
19. ((energy or oxygen) adj expenditure).ti,ab. (14,885)
20. or/17-19 (17,369)
21. 16 not 20 (593,002)
22. animal/ or animal experiment/ (3,059,048)
23. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (4,688,188)
24. or/22-23 (4,688,188)
25. exp human/ or human experiment/ (12,277,839)

26. 24 not (24 and 25) (3,764,868)
27. 21 not 26 (567,207)
28. Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88,290)
29. Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18,423)
30. Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32,909)
31. (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (39,414)
32. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj3 (allerg$ or Hypersensiti$ or hyper-sensiti$)).ti,ab,ot,hw. (5959)
33. ((severe$ or severity or worse$ or acute$ or emergenc$ or urgen$ or grave$ or serious$ or dangerous$ or life-threat$ or lifethreat$ or potentially fatal$) adj2 (systemic$ or allerg$ or skin$ or dermatolog$ or cutaneous$) adj2 (reaction$ or effect$ or event$ or rash$)).ti,ot,ab. (3063)
34. or/28-33 (137,588)
35. 27 and 34 (5617)

Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: Embase (Ovid) weekly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 17 March 2011]. Available from: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase

Health Technology Assessment (HTA) (Internet): 2000 to 16 March 2011 www.crd.york.ac.uk/crdweb/

Searched 17 March 11

1. MeSH Hypersensitivity (51)
2. MeSH Drug hypersensitivity (29)
3. MeSH Hypersensitivity, immediate (7)
4. MeSH Anaphylaxis (17)
5. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
6. MeSH food hypersensitivity (14)
7. MeSH alveolitis, extrinsic allergic (0)
8. MeSH aspergillosis, allergic bronchopulmonary (0)
9. MeSH latex hypersensitivity (5)
10. Anaphyla* OR pseudoanaphyla* (80)
11. (severe* NEAR allerg*) OR (severity NEAR allerg*) OR (worse* NEAR allerg*) OR (acute* NEAR allerg*) (117)
12. (emergenc* NEAR allerg*) OR (urgen* NEAR allerg*) OR (grave* NEAR allerg*) OR (serious* NEAR allerg*) (50)
13. (dangerous* NEAR allerg*) OR (life-threat* NEAR allerg*) OR (lifethreat* NEAR allerg*) OR (potentially AND fatal* NEAR allerg*) (12)
14. (severe* NEAR Hypersensiti*) OR (severity NEAR Hypersensiti*) OR (worse* NEAR Hypersensiti*) OR (acute* NEAR Hypersensiti*) 29)
15. (emergenc* NEAR Hypersensiti*) OR (urgen* NEAR Hypersensiti*) OR (grave* NEAR Hypersensiti*) OR (serious* NEAR Hypersensiti*) (11)
16. (dangerous* NEAR Hypersensiti*) OR (life-threat* NEAR Hypersensiti*) OR (lifethreat* NEAR Hypersensiti*) OR (potentially AND fatal* NEAR Hypersensiti*) (5)
17. (severe* NEAR Hyper-sensiti*) OR (severity NEAR Hyper-sensiti*) OR (worse* NEAR Hyper-sensiti*) OR (acute* NEAR Hyper-sensiti*) 29)
18. (emergenc* NEAR Hyper-sensiti*) OR (urgen* NEAR Hyper-sensiti*) OR (grave* NEAR Hyper-sensiti*) OR (serious* NEAR Hyper-sensiti*) (11)

19. (dangerous* NEAR Hyper-sensiti*) OR (life-threat* NEAR Hyper-sensiti*) OR (lifethreat* NEAR Hyper-sensiti*) OR (potentially AND fatal* NEAR Hyper-sensiti*) (5)
20. (severe* NEAR Systemic*) OR (severity NEAR Systemic*) OR (worse* NEAR Systemic*) OR (acute* NEAR Systemic*) (180)
21. (emergenc* NEAR Systemic*) OR (urgen* NEAR Systemic*) OR (grave* NEAR Systemic*) OR (serious* NEAR Systemic*) (41)
22. (dangerous* NEAR Systemic*) OR (life-threat* NEAR Systemic*) OR (lifethreat* NEAR Systemic*) OR (potentially AND fatal* NEAR Systemic*) (18)
23. (dangerous* NEAR Skin) OR (life-threat* NEAR Skin) OR (lifethreat* NEAR Skin) OR (potentially AND fatal* NEAR Skin) (14)
24. (severe* NEAR Skin) OR (severity NEAR Skin) OR (worse* NEAR Skin) OR (acute* NEAR Skin) (175)
25. (emergenc* NEAR Skin) OR (urgen* NEAR Skin) OR (grave* NEAR Skin) OR (serious* NEAR Skin) (85)
26. (severe* NEAR Dermatolog*) OR (severity NEAR Dermatolog*) OR (worse* NEAR Dermatolog*) OR (acute* NEAR Dermatolog*) (41)
27. (emergenc* NEAR Dermatolog*) OR (urgen* NEAR Dermatolog*) OR (grave* NEAR Dermatolog*) OR (serious* NEAR Dermatolog*) (7)
28. (dangerous* NEAR Dermatolog*) OR (life-threat* NEAR Dermatolog*) OR (lifethreat* NEAR Dermatolog*) OR (potentially AND fatal* NEAR Dermatolog*) (0)
29. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (521)
30. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (808)
31. (econom* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR budget*) (35,538)
32. (expenditure* NOT energy) (738)
33. (value NEAR money) (204)
34. #31 or #32 or #33 (35,555)
35. #30 and #34 (396)

The HTA search retrieved 28 records.

NHS Economic Evaluation Database (NHS EED) (Internet): 2000 to 16 March 2011 www.crd.york.ac.uk/crdweb/

Searched 17 March 2011

1. MeSH Hypersensitivity (51)
2. MeSH Drug hypersensitivity (29)
3. MeSH Hypersensitivity, immediate (7)
4. MeSH Anaphylaxis (17)
5. MeSH Drug Eruptions EXPLODE 1 2 3 (12)
6. MeSH food hypersensitivity (14)
7. MeSH alveolitis, extrinsic allergic (0)
8. MeSH aspergillosis, allergic bronchopulmonary 0)
9. MeSH latex hypersensitivity (5)
10. Anaphyla* OR pseudoanaphyla* (80)
11. (severe* NEAR allerg*) OR (severity NEAR allerg*) OR (worse* NEAR allerg*) OR (acute* NEAR allerg*) (117)
12. (emergenc* NEAR allerg*) OR (urgen* NEAR allerg*) OR (grave* NEAR allerg*) OR (serious* NEAR allerg*) (50)
13. (dangerous* NEAR allerg*) OR (life-threat* NEAR allerg*) OR (lifethreat* NEAR allerg*) OR (potentially AND fatal* NEAR allerg*) (12)
14. (severe* NEAR Hypersensiti*) OR (severity NEAR Hypersensiti*) OR (worse* NEAR Hypersensiti*) OR (acute* NEAR Hypersensiti*) (29)

15. (emergenc* NEAR Hypersensiti*) OR (urgen* NEAR Hypersensiti*) OR (grave* NEAR Hypersensiti*) OR (serious* NEAR Hypersensiti*) (11)
16. (dangerous* NEAR Hypersensiti*) OR (life-threat* NEAR Hypersensiti*) OR (lifethreat* NEAR Hypersensiti*) OR (potentially AND fatal* NEAR Hypersensiti*) (5)
17. (severe* NEAR Hyper-sensiti*) OR (severity NEAR Hyper-sensiti*) OR (worse* NEAR Hyper-sensiti*) OR (acute* NEAR Hyper-sensiti*) (29)
18. (emergenc* NEAR Hyper-sensiti*) OR (urgen* NEAR Hyper-sensiti*) OR (grave* NEAR Hyper-sensiti*) OR (serious* NEAR Hyper-sensiti*) (11)
19. (dangerous* NEAR Hyper-sensiti*) OR (life-threat* NEAR Hyper-sensiti*) OR (lifethreat* NEAR Hyper-sensiti*) OR (potentially AND fatal* NEAR Hyper-sensiti*) (5)
20. (severe* NEAR Systemic*) OR (severity NEAR Systemic*) OR (worse* NEAR Systemic*) OR (acute* NEAR Systemic*) (180)
21. (emergenc* NEAR Systemic*) OR (urgen* NEAR Systemic*) OR (grave* NEAR Systemic*) OR (serious* NEAR Systemic*) (41)
22. (dangerous* NEAR Systemic*) OR (life-threat* NEAR Systemic*) OR (lifethreat* NEAR Systemic*) OR (potentially AND fatal* NEAR Systemic*) (18)
23. (dangerous* NEAR Skin) OR (life-threat* NEAR Skin) OR (lifethreat* NEAR Skin) OR (potentially AND fatal* NEAR Skin) (14)
24. (severe* NEAR Skin) OR (severity NEAR Skin) OR (worse* NEAR Skin) OR (acute* NEAR Skin) (175)
25. (emergenc* NEAR Skin) OR (urgen* NEAR Skin) OR (grave* NEAR Skin) OR (serious* NEAR Skin) (85)
26. (severe* NEAR Dermatolog*) OR (severity NEAR Dermatolog*) OR (worse* NEAR Dermatolog*) OR (acute* NEAR Dermatolog*) (41)
27. (emergenc* NEAR Dermatolog*) OR (urgen* NEAR Dermatolog*) OR (grave* NEAR Dermatolog*) OR (serious* NEAR Dermatolog*) (7)
28. (dangerous* NEAR Dermatolog*) OR (life-threat* NEAR Dermatolog*) OR (lifethreat* NEAR Dermatolog*) OR (potentially AND fatal* NEAR Dermatolog*) (0)
29. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 (521)
30. #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 (808)

The NHS EED search retrieved 299 records.

Science Citation Index (SCI) (Web of Science): 1970 to 12 February 2011

Searched 14 February 2011

17 492 #6 and #16
Databases = SCI-EXPANDED Timespan = All Years

16 >100,000 #11 not #15
Databases = SCI-EXPANDED Timespan = All Years

15 31,011 #12 or #13 or #14
Databases = SCI-EXPANDED Timespan = All Years

14 19,066 TS = ((energy or oxygen) SAME expenditure)
Databases = SCI-EXPANDED Timespan = All Years

13 1,447 TS = (metabolic SAME cost)
Databases = SCI-EXPANDED Timespan = All Years

12 11,824 TS = ((energy or oxygen) SAME cost)
Databases = SCI-EXPANDED Timespan = All Years

11 >100,000 #7 or #8 or #9 or #10
Databases = SCI-EXPANDED Timespan = All Years

10 41,609 TS = budget*
Databases = SCI-EXPANDED Timespan = All Years

9 886 TS = (value SAME money)
Databases = SCI-EXPANDED Timespan = All Years

8 12,743 TS = (expenditure* not energy)
Databases = SCI-EXPANDED Timespan = All Years

7 >100,000 TS = (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*)
Databases = SCI-EXPANDED Timespan = All Years

6 23,983 #4 not #5
Databases = SCI-EXPANDED Timespan = All Years

5 >100,000 TS = (cat or cats or dog or dogs or animal or animals or rat or rats or hamster or hamster or feline or ovine or canine or bovine or sheep)
Databases = SCI-EXPANDED Timespan = All Years

4 28,875 #1 or #2 or #3
Databases = SCI-EXPANDED Timespan = All Years

3 7,739 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (systemic* or allerg* or skin* or dermatolog* or cutaneous*) SAME (reaction* or effect* or event* or rash*))
Databases = SCI-EXPANDED Timespan = All Years

2 8,259 TS = ((severe* or severity or worse* or acute* or emergenc* or urgen* or grave* or serious* or dangerous* or life-threat* or lifethreat* or potentially fatal*) SAME (allerg* or Hypersensiti* or hyper-sensiti*))
Databases = SCI-EXPANDED Timespan = All Years

1 16,857 TS = (Anaphyla* or pseudoanaphyla*)
Databases = SCI-EXPANDED Timespan = All Years

Based on Costs filter: Centre for Reviews and Dissemination. NHS EED Economics Filter: Medline (Ovid) monthly search [Internet]. York: Centre for Reviews and Dissemination; 2010 [cited 13 January 2011]. Available from: www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED

Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCOhost): 1981 to 18 February 2011

Searched 23 February 2011
S13 s9 and s12 Limiters - Exclude MEDLINE records (651)

S12 s10 not s11 (158,410)

S11 TX (energy N3 cost) or (oxygen N3 cost) or (energy N3 expenditure) or (oxygen N3 expenditure) or (metabolic N3 cost) (2620)

S10 TX (value N3 money) or TX ((expenditure* not energy)) or TX ((economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or budget*)) (159,067)

S9 s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 (30,528)

S8 TX (severe* N2 rash*) or (severity N2 rash*) or (worse* N2 rash*) or (acute* N2 rash*) or (emergenc* N2 rash*) or (urgen* N2 rash*) or (grave* N2 rash*) or (serious* N2 rash*) or (dangerous* N2 rash*) or (life-threat* N2 rash*) or (lifethreat* N2 rash*) or (potentially N3 fatal* N2 rash*) (97)

S7 TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) TX ((severe* N2 reaction*) or (severity N2 reaction*) or (worse* N2 reaction*) or (acute* N2 reaction*) or (emergenc* N2 reaction*) or (urgen* N2 reaction*) or (grave* N2 reaction*) or (serious* N2 reaction*) or (dangerous* N2 reaction*) or (life-threat* N2 reaction*) or (lifethreat* N2 reaction*) or (potentially N3 fatal* N2 reaction*)) or TX ((severe* N2 effect*) or (severity N2 effect*) or (worse* N2 effect*) or (acute* N2 effect*) or (emergenc* N2 effect*) or (urgen* N2 effect*) or (grave* N2 effect*) or (serious* N2 effect*) or (dangerous* N2 effect*) or (life-threat* N2 effect*) or (lifethreat* N2 effect*) or (potentially N3 fatal* N2 effect*)) or TX ((severe* N2 event*) or (severity N2 event*) or (worse* N2 event*) or (acute* N2 event*) or (emergenc* N2 event*) or (urgen* N2 event*) or (grave* N2 event*) or (serious* N2 event*) or (dangerous* N2 event*) or (life-threat* N2 event*) or (lifethreat* N2 event*) or (potentially N3 fatal* N2 event*)) (9240)

S6 TX ((severe* N3 allerg*) or (severity N3 allerg*) or (worse* N3 allerg*) or (acute* N3 allerg*) or (emergenc* N3 allerg*) or (urgen* N3 allerg*) or (grave* N3 allerg*) or (serious* N3 allerg*) or (dangerous* N3 allerg*) or (life-threat* N3 allerg*) or (lifethreat* N3 allerg*) or (potentially N3 fatal* N3 allerg*)) or TX ((severe* N3 hypersensiti*) or (severity N3 hypersensiti*) or (worse* N3 hypersensiti*) or (acute* N3 hypersensiti*) or (emergenc* N3 hypersensiti*) or (urgen* N3 hypersensiti*) or (grave* N3 hypersensiti*) or (serious* N3 hypersensiti*) or (dangerous* N3 hypersensiti*) or (life-threat* N3 hypersensiti*) or (lifethreat* N3 hypersensiti*) or (potentially N3 fatal* N3 hypersensiti*)) or TX ((severe* N3 hyper-sensiti*) or (severity N3 hyper-sensiti*) or (worse* N3 hyper-sensiti*) or (acute* N3 hyper-sensiti*) or (emergenc* N3 hyper-sensiti*) or (urgen* N3 hyper-sensiti*) or (grave* N3 hyper-sensiti*) or (serious* N3 hyper-sensiti*) or (dangerous* N3 hyper-sensiti*) or (life-threat* N3 hyper-sensiti*) or (lifethreat* N3 hyper-sensiti*) or (potentially N3 fatal* N3 hyper-sensiti*)) (711)

S5 TI (Anaphyla* or pseudoanaphyla*) or AB (Anaphyla* or pseudoanaphyla*) (1234)

S4 (MH "Latex Hypersensitivity") (1229)

S3 (MH "Food Hypersensitivity+") (1992)

S2 (MH "Drug Hypersensitivity") (1362)

S1 (MH "Hypersensitivity, Immediate+") (20,402)

Appendix 2 Quality of evidence of included studies

The criteria used in this checklist are adapted from Hayden *et al.*[51]

Cianferoni 2004[3]	
1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Unclear Not reported if all available patients were included in previous study and how the patients for this study were selected
2. Loss to follow-up is unrelated to key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias	Yes Results for all patients included in this study were reported
3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	N/A
4. The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes Definition of recurrence given
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N/A
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes Risk of recurrence presented as percentage
Decker 2008[4]	
1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes All patients who met pre-specified criteria in a certain period were included. Key characteristics are reported and representative
2. Loss to follow-up is unrelated to key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias	Yes Results for all patients included in this study were reported
3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	N/A
4. The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear No definition of recurrence given in this abstract
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N/A
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes Risk of recurrence presented as percentage and relative risk

Mehl 2005[5]	
1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes All patients who met pre-specified criteria in a certain period were included. Key characteristics are reported and representative
2. Loss to follow-up is unrelated to key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias	Yes Results for all patients included in this study were reported
3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	N/A
4. The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear No definition of recurrence given
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N/A
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes Risk of recurrence presented as percentage
Múgica Garcia 2010[6]	
1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	No Cohort of previous study contacted (58.7% response rate). No details on age, sex, weight and ethnicity
2. Loss to follow-up is unrelated to key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias	Yes Results for all patients included in this study were reported
3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	N/A
4. The outcome of interest is adequately measured in study participants, sufficient to limit bias	Yes Definition of recurrence given
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N/A
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes Risk of recurrence presented as percentage

Mullins 2003[7]	
1. The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results	Yes All patients referred for evaluation of possible anaphylaxis were included. Key characteristics are reported and representative
2. Loss to follow-up is unrelated to key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias	Yes Results for all patients included in this study were reported
3. The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias	N/A
4. The outcome of interest is adequately measured in study participants, sufficient to limit bias	Unclear No definition of recurrence given
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	N/A
6. The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results	Yes Risk of recurrence presented as percentage and as risk per patient-years

N/A, not applicable.

Appendix 3 List of studies with rationale for inclusion or exclusion

List of included studies

Risk of recurrence

1. Cianferoni A, Novembre E, Pucci N, Lombardi E, Bernardini R, Vierucci A. Anaphylaxis: a 7-year follow-up survey of 46 children. *Ann Allergy Asthma Immunol* 2004;**92**:464–8.
2. Decker KW, Bellolio MF, Campbell RL, Luke A, Anderson JL, Sauver J, *et al.* Recurrent anaphylaxis events in patients presenting to the emergency department over a 10-year period. *Ann Emerg Med* 2008;**51**:214.
3. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children--a questionnaire-based survey in Germany. *Allergy* 2005;**60**:1440–5.
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Appendix 4 Economic evaluation quality assessment

Quality assessment item		Krasnick 1996[10]	Shaker 2007[9]	Desai and Carroll 2009[8]
Study design				
(1)	The research question is stated	Yes	Yes	Yes
(2)	The economic importance of the research question is stated	No	No	Yes
(3)	The viewpoint(s) of the analysis is clearly stated and justified	No	No	No
(4)	The rationale for choosing the alternative programmes or interventions compared is stated	No	No	No
(5)	The alternatives being compared are clearly described	Yes	No	No
(6)	The form of economic evaluation used is stated	No	Yes	Yes
(7)	The choice of form of economic evaluation is justified in relation to the questions addressed	No	Yes	No
Data collection				
(8)	The source(s) of effectiveness estimates used are stated	Yes	Yes	No
(9)	Details of the design and results of effectiveness study are given (if based on a single study)	No	Unclear	No
(10)	Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	No	No	No
(11)	The primary outcome measure(s) for the economic evaluation is clearly stated	Yes	Yes	No
(12)	Methods to value health states and other benefits are stated	No	Yes	No
(13)	Details of the subjects from whom valuations were obtained are given	Yes	No	No
(14)	Productivity changes (if included) are reported separately	No	No	No
(15)	The relevance of productivity changes to the study question is discussed	No	No	No
(16)	Quantities of resources are reported separately from their unit costs	Yes	No	No
(17)	Methods for the estimation of quantities and unit costs are described	No	No	No
(18)	Currency and price data are recorded	Yes	Yes	No
(19)	Details of currency of price adjustments for inflation or currency conversion are given	No	No	No
(20)	Details of any model used are given	No	Yes	No
(21)	The choice of model used and the key parameters on which it is based are justified	No	No	No

Quality assessment item	Krasnick 1996[10]	Shaker 2007[9]	Desai and Carroll 2009[8]
Analysis and interpretation of results			
(22) Time horizon of costs and benefits is stated	No	Yes	No
(23) The discount rate(s) is stated	No	Yes	No
(24) The choice of rate(s) is justified	No	Yes	No
(25) An explanation is given if costs or benefits are not discounted	No	No	No
(26) Details of statistical tests and CIs are given for stochastic data	No	No	No
(27) The approach to sensitivity analysis is given	No	Yes	No
(28) The choice of variables for sensitivity analysis is justified	No	Yes	No
(29) The ranges over which the variables are varied are stated	No	Yes	No
(30) Relevant alternatives are compared	Yes	Yes	No
(31) Incremental analysis is reported	No	Yes	No
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Yes	No	No
(33) The answer to the study question is given	Yes	Yes	Yes
(34) Conclusions follow from the data reported	Yes	Yes	Yes
(35) Conclusions are accompanied by the appropriate caveats	No	No	No

Appendix 5 Table of model parameters

No.	Parameter	Name of parameter in model	Distribution type	Minimum	Most likely	Maximum	Sources
Population characteristics (see* Chapter 4, Methods of cost-effectiveness analysis*)							
1	Cohort start age	startage	N/A		30		Assumption
2	Proportion of cohort male	pmale			0.5		Health Hospital Episode Statistics (see *Chapter 4, Methods of cost-effectiveness analysis*)
Rate of recurrence (see* Chapter 4, Methods of cost-effectiveness analysis*)							
3	Annual rate of recurrence of anaphylaxis due to drugs with SSs	dprecurdrugSS	Triangular	0	0.001	0.002	Expert opinion
4	Annual rate of recurrence of anaphylaxis due to food with SSs	dprecurfoodSS		0	0.01	0.02	Expert opinion and based on Ewan and Clark 2001[33] [p. 753 text: paragraph heading: 'Severity of follow-up reaction'. No one with a severe initial reaction ($n = 49$) had a further severe reaction]. Ewan and Clark 2005[34] [table 1, p. 112: Severe follow-up reaction grade 5 $r = 3$ (0.5%), $n = 567$ (100%)]
5	Annual rate of recurrence of anaphylaxis due to food with SC	drecurfood		0.05	0.11	0.16	Expert opinion and based on Mullins 2003[7] (figure 1, p. 1037)
6	Annual rate of recurrence of idiopathic anaphylaxis with SC	drecuridio		0.05	0.28	0.51	Expert opinion and based on Mullins 2003[7] (figure 1, p. 1037)
7	Annual rate of recurrence of anaphylaxis due to drugs with SC	drecurdrug		0.05	0.12	0.19	Expert opinion and based on Mullins 2003[7] (figure 1, p. 1037)
8	Annual rate of recurrence of anaphylaxis due to insect sting with SC	drecurinsect		0.05	0.10	0.15	Expert opinion and based on Gonzalez-Perez 2010[15] (pp. 1101–2. Last paragraph, p. 1101: 'Anaphylaxis is associated with high risk of recurrence but is highly unpredictable. Estimated rate: 0.06 to 0.11 episodes per year')

N/A, not applicable.

No.	Parameter	Name parameter in model	Distribution type	*r* in categories	*n*	*r*	Sources
***Trigger probability* (*see* Chapter 4, Methods of cost-effectiveness analysis)**							
9	Probability incidence due to idiopathic	didio	Beta		343	103	Gonzalez-Perez 2010[15] (table V, p. 1104) = 30%
10	Probability incidence due to insect given not idiopathic	dinsect			240	46	Gonzalez-Perez 2010[15] (table V, p. 1104) = 13.4%
11	Probability incidence due to drug given not idiopathic and not insect in child	ddrugchild			87	19	Capps *et al*. 2010[36] (table 1, p. 655) = 12.4%
12	Probability incidence due to drug given not idiopathic and not insect in adult	ddrugadult			303	236	Capps *et al*. 2010[36] (table 1, p. 655) = 44.1%
***Mortality* (*see* Chapter 4, Methods of cost-effectiveness analysis)**							
13	Annual probability of dying given anaphylaxis and presence of emergency services and current AI use	ddieanaph	Beta		3517	20	Soar *et al*. 2008,[17] HES 2010[32]
				r in categories (2.1–4.5, 4.6–9.9, 10–20 and > 20 minutes)			
14	Time to die, food	dtimediefood	Dirichlet	(0; 0; 9; 50)			Soar *et al*. 2008[17]
15	Time to die, drug	dtimediedrug		(0; 2; 4; 7)			Soar *et al*. 2008[17]
16	Time to die, insect	dtimedieinsect		(2; 420; 19)			Soar *et al*. 2008[17]
				r in categories (<8, 8–18 and > 18 minutes)			
17	Ambulance response time, Category A	dtimeA	Dirichlet	(1,442,519; 437,973; 60,160)		N/A	NHS Information Centre 2010[40]
18	Ambulance response time, Category B	dtime19B	Beta		2,559,126	2,322,793	NHS Information Centre 2010[40]

N/A, not applicable.

No.	Parameter	Name parameter in model	Distribution type	*n*	*r*	Minimum	Most likely	Maximum	Sources
19	Probability of correct use of injector with SC	dpinjector	Beta	116	53				Capps *et al*. 2010[36] (*n* = table 3, p. 655 at any time *r* = before ambulance arrived)
20	Probability use injector correctly with SC in child	dinjectorchild		15	10				Capps *et al*. 2010[36] [*n* = table 3, p. 655, at any time *r* = before ambulance arrived (child)]
21	Probability use injector correctly with SC in adult	dinjectoradult		101	43				Capps *et al*. 2010[36] [*n* = table 3, p. 655, *r* = before ambulance arrived (adult)]
22	Probability use injector correctly with SSs	dpinjectorSS	Triangular				1		Assumption
Idiopathic treatment (see* Chapter 4, Methods of cost-effectiveness analysis*)									
23	Median time to remission in frequent idiopathic	dmedianfreq	Triangular			2	4	6	Based on data from Krasnick *et al*. 1996[10]
24	Median time to remission in infrequent idiopathic	dmedianinfreq				1	1.5	2	Based on data from Krasnick *et al*. 1996[10]
25	Proportion of idiopathic that are frequent	dfreqidio	Beta	56	28				Krasnick *et al*. 1996[10]
Venom immunotherapy (see* Chapter 4, Methods of cost-effectiveness analysis*)									
26	Effectiveness of VIT	dpeffectVIT	Triangular			0.75	0.85	0.95	Based on Krishna *et al*. 2010[42]
27	Dropout of VIT	dropout				0.1	0.2	0.3	Based on Goldberg *et al*. 2000[43]
28	Uptake of VIT	duptakeVIT				0.4	0.6	0.8	Based on Cox *et al*. 2011[25]
Utility (see* Chapter 4, Methods of cost-effectiveness analysis*)									
29	Utility decrement due to at risk	duatrisk	Triangular			0.06	0.08	0.1	Based on Voordouw *et al*. 2010[45]
30	Duration of recurrence	ddurationrecur	Uniform			1	N/A	9	Based on Neuner *et al*. 2003[46]
31	Utility factor with SSs	duSSimprove	Triangular			0	0.25	0.5	Assumption based on expert opinion
32	Utility factor with AI	duAIimprove				0	0.25	0.5	Assumption based on expert opinion

N/A, not applicable.

No.	Parameter	Name of parameter in model	Distribution type	Mean	Standard error[a]	Minimum	Most likely	Maximum	Sources
Costs (see* Chapter 4, Methods of cost-effectiveness analysis*)									
33	Mean cost of inpatient care	dcostrecur	Normal	£469.88	£37.585				HES 2010[32]
34	Mean cost of AI	cinjector	N/A	£28.97	N/A				BNF 61[18]
35	Costs of two SS sessions (each about £200)	cSS	N/A	£400	N/A				Expert opinion (Commissioner in UK)
36	Duration of VIT (years)	ddurationVIT	Triangular			2	3	4	Based on Diwaker *et al*. 2008[48]
37	Induction phase of VIT (build-up) (weeks) average cost for bee and wasp extract	dbuildupVIT	Triangular			8	10	12	Based on Cox *et al*. 2011[25] Expert opinion
38	For VIT maintenance treatment average cost for bee and wasp extract	cVITmaintenance	N/A	£60	N/A				BNF 61[18]
39	For VIT induction treatment	cVITinitial	N/A	£70	N/A				BNF 61[18]
40	Number of weeks between VIT maintenance doses	nVITmaintenance	Triangular			4	6	8	Expert opinion and Cox *et al*. 2011[25]
41	Cost of prednisolone per mg	cpred	N/A	£0.02	N/A				BNF 61[18]
42	Duration of prednisolone course in months	ddurationpred	Uniform			2	N/A	3	Simons *et al*. 2010[27]
43	Start dose of prednisolone in mg	dstartdosepred	Uniform			60	N/A	100	Simons *et al*. 2010,[27] Lieberman *et al*. 2010[24]
44	Duration of start dose of prednisolone	dstartduration	Uniform			1	N/A	2	Simons *et al*. 2010,[27] Lieberman *et al*. 2010[24]

N/A, not applicable.

EME
HS&DR
HTA
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PHR

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