

Appendix G

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Assessment Report Guide

Title: Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode.

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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It should be noted that this project is addressing only a part of the clinical guidance referred to in the title. The EAG was asked to support preparation of this clinical guidance, i.e. to prepare a clinical review to address four questions and a cost-effectiveness analysis to address two questions. Therefore, this report will focus on these specific questions: see the protocol (<http://www.hta.ac.uk/protocols/201001580001.pdf>) for details. Also, the executive summary, background, assessment of factors relevant to the NHS and other parties, final discussion and conclusions were deemed to be not applicable.

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1. DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness-analysis
CENTRAL	Cochrane Central Register of Controlled Trials
DARE	Database of Abstracts of Reviews of Effects
EAG	Evidence Assessment Group
GIN	International Guidelines Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
PICO	Population, intervention, comparison, outcome
SS	Specialist service
AI	Adrenaline injector
SC	Standard care
GP	General practitioner
BNF	British National Formulary
PCA	Prescription Cost Analysis
NHS	National Health Service
DAM	Decision Analytic Model
ED	Emergency department
UK	United Kingdom
VIT	Venom immunotherapy

2. EXECUTIVE SUMMARY

Not applicable.

3. BACKGROUND

Not applicable

4. DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

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.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

This guideline was developed in accordance with the process for short clinical guidelines set out in 'The guidelines manual' (2009) (see www.nice.org.uk/GuidelinesManual). There is more information about how NICE clinical guidelines are developed on the NICE website (www.nice.org.uk/HowWeWork). A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' (fourth edition, published 2009), is available from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1739).

5.1 Methods for reviewing effectiveness

- 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). The aim of the systematic searches was to comprehensively identify the published evidence to answer the review questions developed by the Guideline Development Group 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 imposed on the searches.

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

Guideline Development Group members were also asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

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); browsing or simple search strategies were employed. The search results were used to provide information for scope development and project planning.

Guidance/guidelines	Systematic reviews/ economic evaluations
Cochrane Central Register of Controlled Trials – CENTRAL	International Guidelines 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	

Table 1: sources of guidance/guidelines

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 (CRD)
- Health Technology Assessment Database – HTA (CRD)
- NHS Economic Evaluation Database – NHS EED (CRD)
- Science Citation Index – SCI (Web of Science)
- CINAHL (EBSCO)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

- Inclusion and exclusion criteria

Participants

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

Setting

Relevant settings are 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 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 will be 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 will also be considered if reported:

- Acceptability of tests to patients
- Adverse events associated with testing

Study designs

The following types of studies will be included:

- Randomised or non-randomised controlled trials.
- 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 will be 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). These tables can be found in chapter 5.2.
 - **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). These tables can be found in appendix 2.
 - **Methods of data synthesis**
Not applicable

5.2 Results

5.2.1 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 screened. Five studies were included with another 60 studies highlighted as possibly relevant for the background and/or the cost-effectiveness-analysis (CEA). A flow chart of the screening process is presented below.

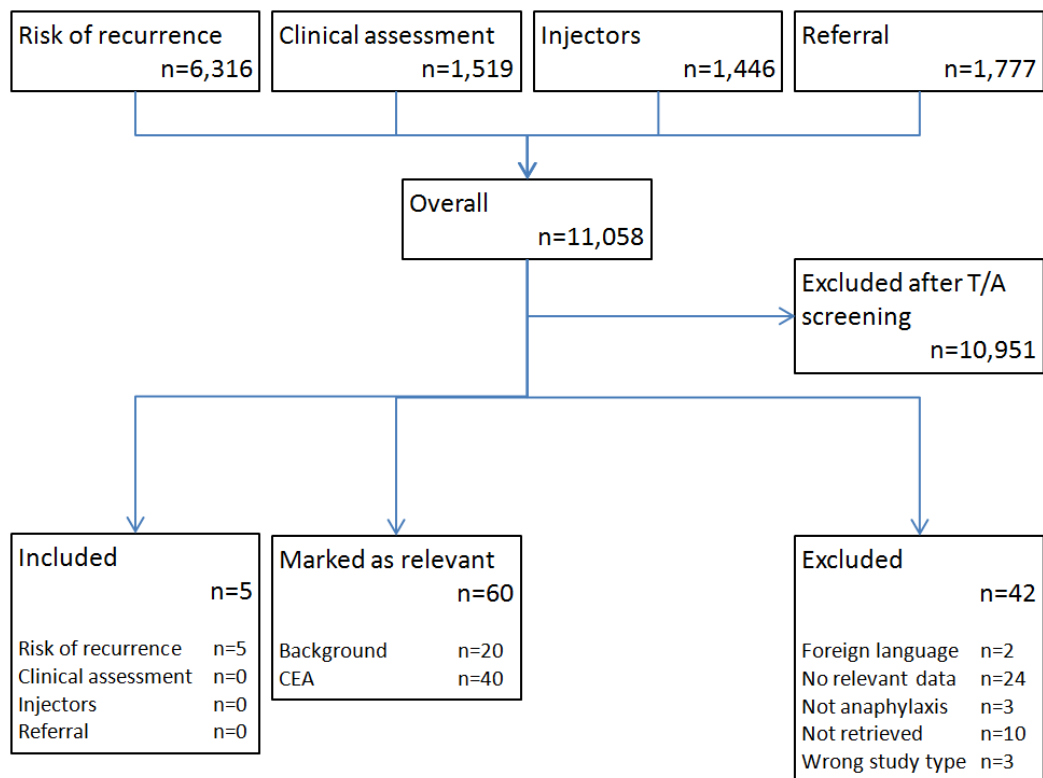


Figure 1: flow chart of study identification

5.2.2 Assessment of effectiveness

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 Table 3.

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
Cianferoni 2004	Cianferoni, A., E. Novembre, et al. (2004). "Anaphylaxis: a 7-year follow-up survey of 46 children." <i>Annals of Allergy Asthma & Immunology</i> 92(4): 464-468.	Observational retrospective	Low risk of bias but unclear how patients were selected	<p>Recurrence defined as the presence of another anaphylaxis episode: at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents.</p> <p>Defined risk factors for recurrence: history of atopic dermatitis, current urticaria/angioedema, history to sensitivity to 1 food allergen.</p>	7 yrs (SD 1 yr, range 5-8.6 yrs)	N/R
Decker	Decker, K. W., M. F. Bellolio, et al. (2008).	Observational	Low risk of bias but no	No details provided	Mean 1.1 yrs (range 7 days to	N/R

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
2008	"Recurrent anaphylaxis events in patients presenting to the emergency department over a 10-year period." <i>Annals of Emergency Medicine</i> 51(4): 214.	prospective	definition of recurrence given.		13 yrs)	
Mehl 2005	Mehl, A., U. Wahn, et al. (2005). "Anaphylactic reactions in children--a questionnaire-based survey in Germany." <i>Allergy</i> 60(11): 1440-1445.	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, hospitalization and prescribed emergency set after the episode	1 yr (patients identified over a period of 12 mths retrospectively)	Industry: InfectoPharm Arzneimittel und Consilium GmbH, Heppenheim, Germany ('financial support')
Múgica Garcia	Múgica Garcia, M., M. Tejedor Alonso, et al. (2010). A study of the	Observational retrospective	Medium risk of bias as only 58.7 % of	Recurrence defined as any new episode of anaphylaxis,	N/R	N/R

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
2010	recurrence of anaphylaxis. Allergy: European Journal of Allergy and Clinical Immunology. Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom. Conference Publication: (var.pagings). 65 (pp 587), 2010. Date of Publication: June 2010.		previous cohort were included and no details on age, gender, weight and ethnicity were reported.	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 for the recurrence.		
Mullins 2003	Mullins, R. J. (2003). "Anaphylaxis: risk factors for recurrence." Clinical & Experimental Allergy 33(8): 1033-1040.	Observational prospective	Low risk of bias but no definition of recurrence given.	Recurrence presented as proportion of patients relapsing. Rate of recurrence/ 100 patient-years of observation: calculated by dividing the cumulative length of	2.2 yrs	N/R

Study	Bibliographic reference	Study type	Study quality	Outcome measures	Length of follow-up	Source of funding
				observation by the number of recurrences involving that trigger.		
mth(s)= month(s), N/R= not reported, SD= standard deviation, yr(s)= year(s)						

Table 2: Characteristics of included studies

Study	Setting	No. of patients	Patient characteristics	Results
Cianferoni 2004	Primary care, Italy	46 (of 76 from a previous cohort study, re-evaluated after a mean of 7 years) Inclusion for previous study: Patients with anaphylaxis referred to an allergy unit (Florence, Italy) who had at least 2 of the main indicators of anaphylactic reaction (hypotension, inspiratory dyspnea, and urticaria-angioedema) within 2 hours after exposure to one of the most probable causative agents.	Diagnosed anaphylaxis. Mean age 14 yrs (SD 4.92 yrs, range 7-26 yrs). Age at first episode: 5.8 yrs (SD 4.9, 1-18 yrs). 61 % male. No details on weight and ethnicity. Aetiology, ood 19.5% (9/46), exercise 4.4% (2/46), drug 2.2% (1/46), idiopathic 4.4% (2/46).	Risk of recurrence: 30 % (14/46)
Decker 2008	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 years (SD 18.2). 44.1 % male. No further details.	2 nd event in 45/211 (21.3 %). Median time of presentation: 395 days (range 7d-13yrs). 3 rd 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	Primary care,	103 children (<12 yrs)	Median age 5 yrs (range 3mths-12 yrs). 58 % male. No	'No significant difference was found for allergens looking

	Germany	<p>Inclusion: reported accidental anaphylactic reactions occurring during 12 months in infants and children below 12 years of age. Reports reviewed individually by two paediatric allergologists.</p> <p>Exclusion: reported cases excluded if the reported episode was not accidental (e.g. occurred after diagnostic provocation) or if the patient was not under the age of 12.</p>	<p>details on weight and ethnicity. Causative allergen was known or strongly suspected in 95/103 (92 %) of all patients.</p> <p>Overall: Food 57 % (59/103), Insect sting 13 % (13/103), SIT 12 % (12/103), Medication 6% (6/103), Other* 4 % (4/103), Unknown 8 % (9/103).</p> <p>Foods only: 57 % (59/103):</p> <p>Peanut 20 % (12/59), Tree nut 20 % (12/59), Cow's milk 14 % (8/59), Fish 14 % (8/59), Hen's egg 7 % (4/59), Other* 25 % (15/59)</p>	<p>only at severe reactions (grades III and IV)' (no data reported). Age differences:</p> <p>Food, 'patients significantly younger than the overall group' (mean 3.9 yrs, SD 3).</p> <p>SIT, ' significantly older' (mean 9.8 yrs, SD 1.9)</p> <p>Venom, 'patients significantly older' (mean 7.6 yrs, SD 3.2)</p> <p>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)</p>
Múgica Garcia 2010	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, gender, weight and ethnicity.	<p>Overall risk 325/933 (34.8 %).</p> <p>Same type as first episode.</p> <p>Latex: 72.7 %</p> <p>Food: 38.8 %</p>

				Unknown 32.9 % Hymenoptera venom 33.3 %
Mullins 2003	Primary care, Australia	432 patients referred for evaluation of possible anaphylaxis to community-based specialist medical practice between Feb 1995 and July 2000..	Mean age 27.4 yrs (SD 19.5, range: 1-82). 48 % male. No details on weight and ethnicity. 1 st 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 pat-years; Risk of severe recurrence: 10/100 pat-years. Risk factors for recurrence: exercise and idiopathic cause, female gender. Risk of overall recurrence: 57/patient-years Risk of severe recurrence: 10/patient-years 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, mth(s)= month(s), RR= relative risk, SD= standard deviation, SIT= specific immunotherapy, yr(s)= year(s)				

Table 3: Findings of included studies

6. 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 5 for how this was applied to each database). 40 papers were retrieved from title and abstract screening and 3 met the inclusion criteria for design and population.

Two studies were published that reported on economic evaluations in the form of decision analytic models (DAMs) of the use of adrenaline injectors (AIs) (n=2) in a general allergy population (Desai and Carroll 2009) and in patients with a mild venom anaphylaxis (Shaker 2007) in the United States of America. Another American study evaluated the treatment and its related costs in idiopathic anaphylaxis patients (Krasnick et al 1996). All studies reported the costs in US dollar (\$). To assess the quality of these economic evaluations the BMJ checklist was used, including 35 items

(<http://resources.bmj.com/bmj/authors/checklists-forms/health-economics>).

Items scored as 'yes' received one point. Items scored as 'unclear' or 'no' received no points. The BMJ checklist scores were 11 for the study by Krasnick et al. 1996 and 18 points for the study reported by Shaker 2007. The study published by Desai and Carroll 2009 was only reported as a congress abstract, which unsurprisingly resulted in a very low score on the BMJ checklist (5 points out of 35 points). Full details are in Appendix 5.

The study by Boxer et al. was excluded after reading the full text paper as, contrary to the title, no medical costs were reported (Boxer et al. 1989).

Study	Design	Population	Comparators	BMJ checklist
Krasnick et al 1996	Cost description	idiopathic anaphylaxis	before AI implementation compared to after AI implementation	11
Shaker 2007	DAM for CEA	Children with mild venom anaphylaxis	treatment of mild venom anaphylaxis with AI compared to treatment of mild venom anaphylaxis without AI use	18
Desai and Carroll 2009	DAM	Users of AI	Conventional AI (EpiPen compared to a new AI device (intelliject)	5 (congress abstract)

Table 4: summary of economic evaluations on anaphylaxis

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

Krasnick et al 1996

This study was designed to determine the efficacy of a specialist treatment in an University Allergy-Immunology Division using oral corticosteroids, antihistamines, and sympathomimetics for patients with idiopathic anaphylaxis. 225 patients diagnosed with idiopathic anaphylaxis treated in one university hospital from 1971 to 1990 were retrospectively reviewed. The costs of both emergency care (physician fees, medications (intravenous

corticosteroids, subcutaneous epinephrine, and intramuscular diphenhydramine), pulse oximetry, and cardiac monitoring) and hospitalization (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 during the year 1995 (no details on unit costs were reported). Optimal discriminant analyses (ODA) were used to determine whether the treatment protocol made a significant decrease in hospital costs for four subgroups idiopathic anaphylaxis patients. Significant decreases in emergency room visits occurred for three of the four subgroups of idiopathic anaphylaxis patients. Significant decreases in the number of hospitalizations ($P < 0.022$) and intensive care unit admissions ($P < 0.009$) occurred for the idiopathic anaphylaxis patients with generalized symptoms (two subgroups). Overall, there were 165 emergency room evaluations, 17 hospitalizations, and 18 intensive care unit admissions (five requiring intubation) before patients received the specialist treatment at a cost of \$225,000. There were 51 emergency room visits, three hospitalizations, and no intensive care unit admissions after evaluations and treatment the specialist service at an estimated cost of \$40 260, for a savings of \$184, 740.

Shaker 2007

This study was designed to evaluate the cost-effectiveness of the prophylactic self-injectable epinephrine 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 (\$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. 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 \$469,459 per year of life saved and \$6,882,470 per death prevented when evaluated at a 40-year time horizon. The sensitivity analysis revealed that only if the annual fatality rate exceeded 2 per 100,00 persons at risk the use of AI might become cost effective at \$97,146 per life-year saved. 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 less than 2 per 100,000 persons at risk. The source of financial support of this study was not reported.

Desai and Carroll 2009

This study compared the costs and consequences of using an established device (probably the EpiPen) versus a novel device (Intelliject) for treatment of an 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 hospitalizations. The costs included in the model were: costs of device use, ED use and hospitalizations. Data were obtained from literature, an online query tool for Healthcare cost (HCUPnet) and clinical study data of the company who developed the new AI (Intelliject, Inc). 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 hospitalization (7) and fewer hospitalizations (2 vs. 4). The results also indicated higher device costs (\$15,837 vs. \$6,291) and the same ED use costs (\$9,375) but lower costs for hospitalizations (\$15,303 vs. \$30,606); leading to lower total costs of the new device (\$40,515 vs. \$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, higher recovery rate as well as fewer hospitalizations.

Summary

None of these studies is useful in directly addressing the questions regarding SS. However, the study by Krasnick et al 1996 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 2007 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 to our definition of anaphylaxis, which is life-threatening. The study by Desai and Carroll 2009 was unfortunately too poorly reported to be useful.

6.2 Independent economic assessment

The analysis aimed to inform the following two questions:

What is the cost effectiveness of referral to specialist allergy clinics (specialist service (SS)) for the diagnosis of anaphylaxis after 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 injectors (AIs) for the treatment of anaphylaxis including the cost implications of training in the use of the adrenaline injector?

6.2.1 Methods

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[1], which includes the definition of anaphylaxis. For example, Stewart and Ewan[2] 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 SS was (through the GP) 4 out of 24. In a study by El-Shanawany et al[3] 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[4]. However, a more recent study in the UK by Gonzalez-Perez et al[5] produced an estimate of 34.38. The El-Shanawany study also revealed that the rate of referral to SS was zero. Erlewyn-Lajeunesse et al [1] selected cases of asthma, urticarial and allergic reaction as well as anaphylaxis according to physician diagnosis (in the absence of Gold Standard) to test diagnostic criteria. This could imply that the suspected population is composed essentially of those suffering an allergic reaction, but less severe and those with asthma. However, this Guideline definition rules this out by including:

‘...rapidly developing life-threatening airway, breathing and/or circulation problems...’ (Scope, p.1)

This fits with the definition used by Brown et al [6] 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 SS. 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 non-anaphylaxis patients.

However, in the latest UK guidelines for emergency treatment [7] there is a recommendation that all those suffering anaphylaxis should be referred to a SS and there is no mention of the difficulty of deciding which of the suspected those are. 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 SS and SC and not between ‘referral given suspected’, which therefore implies that the population can be assumed to be only those who had an emergency admission for anaphylaxis.

Comparators

The following combinations were considered in the model:

SC no AI: standard care (SC) plus no prescription of adrenaline injectors where standard care is defined as the absence of referral to specialist service (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 (BNF 61) and in several doses, recommended as 500, 300 and 150 micrograms for adults, children aged 6-12 and aged under 6 respectively [7]. 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 the BNF [number 61]). 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 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)[7].

SS no AI: all patients with suspected anaphylaxis are referred to specialist service 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). 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).

SS plus AI: all patients both attend a specialist service and are prescribed adrenaline injectors.

Framework

Given the lack of CEA evidence, a cost-utility analysis [8] was undertaken with costs and quality-adjusted life-years (QALY) considered over patients’ lifetime from a UK NHS perspective in accordance with NICE methods guidance [9]. Costs were in 2011 GBP (£) 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 [10] 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 or older. 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), insect (stings), food and idiopathic [8] (see section on trigger probability below). 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: rate of recurrence, mortality rates, idiopathic treatment and venom immunotherapy, paragraphs; 2.4.2, 2.4.4-2.4.6). The cycle length of the model was set to three months.

A cycle length of 3 months was chosen for convenience in modelling rates of recurrence as probability of a single recurrence event since 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, 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 only, 'remission' (see 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), where recurrence could occur only if remission had not. The possibility of remission for idiopathic was based on two international guidelines [11, 12], where it is suggested that it will occur spontaneously, although those classed as having 'frequent' recurrences (>2 in 2 months or >6 in one year) are recommended to be prescribed prednisolone (see Idiopathic section below).

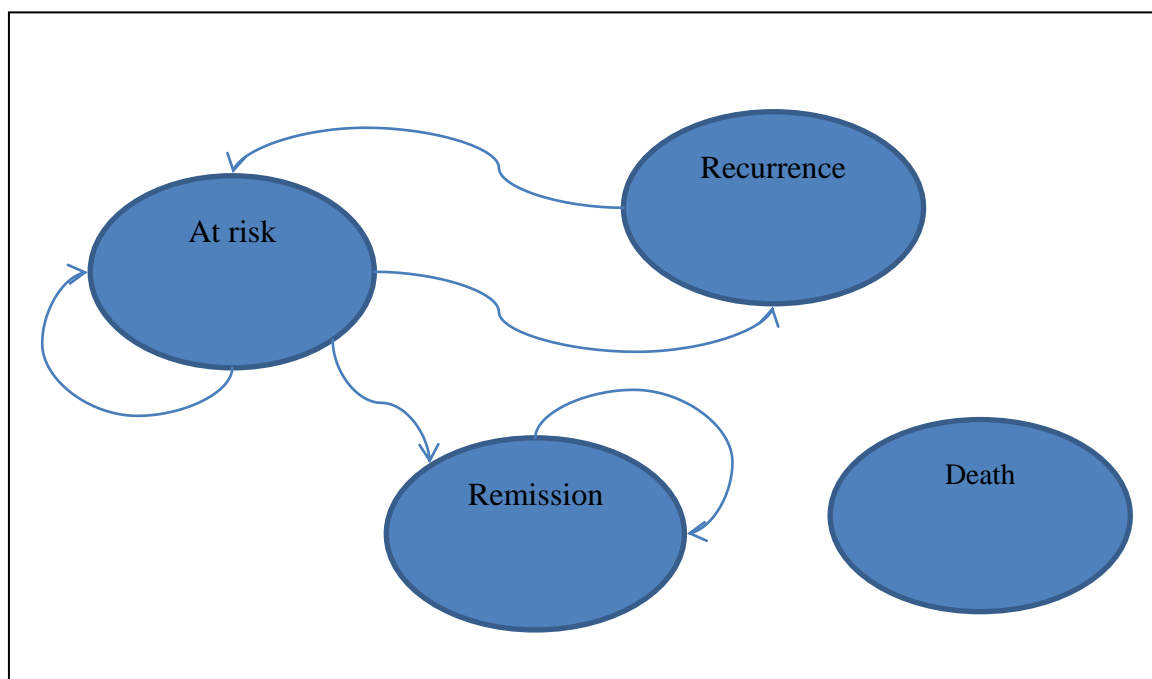


Figure 2: diagram showing the health states and transitions between them: transitions can occur from any live state to the death state.

Those in the 'at risk' or in 'remission' states were assumed to have general population age and gender specific mortality [13]. Those in the 'recurrence' state had this mortality plus an additional probability. Firstly, they were divided into those who used an AI or not, according to a probability for correct use (see section on Mortality below). For both, SS and SC plus AI, this probability was greater than zero since 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 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. With SS, change in recurrence rate depends on cause and is explained below.

Food and Drug

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

Idiopathic

It was assumed that the main effect of SS was treatment of those suffering from frequent episodes of recurrence (see explanation above).

Insect

It was assumed that the main effect of SS was identification and then treatment with *Venom Immunotherapy* (VIT) in accordance with an international guideline [14], guided by expert opinion as to regime. 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, drop out and effectiveness.

Finally, the effect of both SS 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.

Resource use and unit cost estimation

	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
34	mean cost of adrenaline injector	cinjector	n/a	n/a	£28.97	n/a	BNF 61
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
36	Duration of VIT (years)	ddurationVIT	Triangular	2	3	4	Based on Diwaker 2008
37	Induction phase of VIT (build up) (weeks)	dbuildupVIT	Triangular	8	10	12	Based on Cox et al 2011 EO
38	average cost for bee and wasp extract for VIT	cVITmaintenance	n/a	n/a	£60	n/a	BNF 61

	maintenance treatment						
39	average cost for bee and wasp extract for VIT induction treatment	cVITinitial	n/a	n/a	£70	n/a	BNF 61
40	number of weeks between VIT maintenance doses	dnVITmaint	n/a	4	6	8	EO Cox et al 2010
41	Cost of prednisolone per mg	cpred	n/a	n/a	0.02	n/a	BNF 61
42	Duration of prednisolone course in months	ddurationpred	Uniform	2	n/a	3	Simons et al 2010
43	Start dose of prednisolone in mg	dstartdosepred	Uniform	60	n/a	100	Simons et al 2010, Lieberman et al 2010
44	Duration of start dose of prednisolone	dstartduration	Uniform	1	n/a	2	Simons et al 2010, Lieberman et al 2010
45	Number of follow-ups per year for those with a food trigger	nFUfoodSS	n/a	n/a	0.5	n/a	EO**
46	Cost of follow-up for those with a food trigger	cFUfoodSS	n/a	n/a	£200	n/a	EO**

Table 5: cost parameters

*N/A = not applicable, **EO= expert opinion,

Table 5 gives a description of the unit costs (in UK pounds) and resource use data used in the model.

The mean cost and standard error of inpatient care was based on figures for the period of 2009 to 2010 from the Department of Health Hospital Episode Statistics (www.hesonline.nhs.uk) (parameter 33).

The average costs of adrenaline injectors were based on the costs reported in the British National Formulary (BNF61) edition of March 2011 (parameter 34). The life span of an adrenaline-injector was assumed to be 6 months and two prescribed/replaced at a time. The costs of treatment of patients in SS were based on the NHS Reference costs [34]. 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 'multi-professional' categories, for children, Paediatric Clinical Immunology and Allergy (Service code 255) and, for adults, Clinical Immunology and Allergy (Service code 316) (parameter 35). Only those who were prescribed an adrenaline-injector incurred that cost and this was assumed to be for the rest of their life.

Only those with insect trigger and who underwent Venom immunotherapy (VIT) incurred those additional costs (parameters 36-40). Model estimates on current practice of VIT in the UK are based on an audit which evaluated the adherence to international guidelines (Diwaker 2008) [15] and on expert opinion (personal communication (Dr. Pamela Ewan)). Most of the VITs in the UK were given by injection of a purified extract (Pharmalgen), using an

induction scheme of weekly injection for about 10 weeks and continuation for about 3 years, with about a 6 weekly interval during maintenance (Diwaker 2008). In the model a mean duration time of VIT of 3 years with a range of 2 to 4 years is used (Diwaker 2008) (parameter 36). The average costs for bee and wasp extracts used in for VIT were based on the costs reported in the British National Formulary (BNF61) edition of March 2011 (parameter 38-39). The number of weeks between VIT maintenance doses was based on expert opinion and on the American guideline for allergen immunotherapy (Cox et al 2010)[14] (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 (parameters 41-44). The recommendations from two international guidelines [11, 12] for prednisolone is 1-2 weeks every day, starting at 60-100mg, until symptoms are under control and then decreasing over a period of about 2- 3 months. Those with food trigger 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 two years over a lifetime was assumed in the base case (Parameter 45). The cost of each follow-up was also taken from the NHS Reference costs [34] (Parameter 46).

Health measurement estimation

All parameter values were estimated using the best evidence available and according to best practice [9, 16]. Unfortunately, the systematic review revealed only few and generally poor quality studies on rates of recurrence by trigger and none comparing the effectiveness of SS vs SC or the effectiveness of adrenaline injectors, which is confirmed by other recent reviews [7, 17-19]. 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 validate an estimate or to provide an estimate based where possible on the presentation of some evidence.

Because, the latest NICE guidance [9] demands *Probabilistic Sensitivity Analysis* (PSA) [20], 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 [21]. 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 6.

Population characteristics

For the population in the model the following two (parameter 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 counts as a child, we assume that it is less than age 17.

	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 (see section on General model assumptions)

Table 6: population characteristics

Rate of recurrence

	Parameter	Name parameter in model	Distribution type	Min	Most likely	Max	Sources
3	annual rate of recurrence of anaphylaxis due to drugs with <u>SS</u>	dprecurdrugSS	Triangular	0	0.001	0.002	EO*
4	annual rate of recurrence of anaphylaxis due to food with <u>SS</u>	dprecurfoodSS	Triangular	0	0.01	0.02	EO* and based on Ewan et al. 2001: Page 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 Page 112 table 1: Severe follow-up reaction grade 5 r=3 (0.5%), n=567 (100%)
5	annual rate of recurrence of anaphylaxis due to food with <u>SC</u>	drecurfood	Triangular	0.05	0.11	0.16	EO* and based on Mullins 2003, Figure 1, page 1037
6	annual rate of recurrence of idiopathic anaphylaxis with <u>SC</u>	drecuridio	Triangular	0.05	0.28	0.51	EO* and based on Mullins 2003, Figure 1, page 1037
7	annual rate of recurrence of anaphylaxis due to drugs with <u>SC</u>	drecurdrug	Triangular	0.05	0.12	0.19	EO* and based on Mullins 2003, Figure 1, page 1037
8	annual rate of recurrence of anaphylaxis due to insect	drecurinsect	Triangular	0.05	0.10	0.15	EO* and based on Gonzalez-Perez 2010: page 1101-1102

sting with <u>SC</u>							Last paragraph page 1101: "Anaphylaxis is associated with high risk of recurrence but is highly unpredictable. Estimated rate: 0.06 to 0.11 episodes per year"
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Table 7: rates of recurrence

*EO= expert opinion

For the model the annual rate of recurrence for anaphylaxis caused by drugs after referral to specialist service (SS) was based on expert opinions (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 in the same patient again.

Parameter 4, the annual rate of recurrence anaphylaxis due to food in SS 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 allergy (Ewan and Clark, 2001 and 2005) [22]. However, these studies were no 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 value for the annual rate of recurrence of anaphylaxis due to food, drugs and idiopathic (Parameter 5-6) 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 (Mullins 2003) [23]. 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 combinations of figures on incidence of anaphylaxis due to food and exercise induced anaphylaxis (since these were not separated in the report)(Table 8).

	Rate (ppy)**	n	R* per year
meat	0	7	0
soy	12	8	96
cow's milk	11	19	209
crustaceans	7	27	189
fish	3	22	66
wheat+exercise	40	29	1160
fruit/veg+exercise	15	48	720
egg	10	49	490
nuts	9	112	1008

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

** ppy=patient per year, *R= calculated by multiplying the rate, r by the number at risk, n

The average across all foods was calculated by calculating the total annual number (sum across all r per year in the table) and then dividing by the total at risk (summing across all n in the table). The annual rate of recurrence of anaphylaxis due to insect sting induced anaphylaxis (parameter 8) was based on the findings of the most recent (2010) (343 with anaphylaxis) UK study (Gonzalez-Perez 2010) [5] as the figures of the Australian population are not likely to resemble to the UK population, due to the fact that the chance of an insect bite/sting is much higher in Australia compared to the UK. They 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

	Parameter	Name of parameter in model	Distribution type	n	r	Sources
9	probability anaphylaxis idiopathic	didio	Beta*	343	103	Gonzalez-Perez 2010 Table V page 1104 = 30%
10	probability trigger was insect given not idiopathic	dinsect	Beta	240	46	Gonzalez-Perez 2010 Table V page 1104 = 13.41%
11	probability trigger was drug given not idiopathic and not insect in child	ddrugchild	Beta	87	19	Capps et al 2010 Table 1 page 655 = 12.4%
12	probability trigger was drug given not idiopathic and not insect in adult	ddrugadult	Beta	303	236	Capps et al 2010 Table 1 page 655 =44.1%
	probability trigger was food given not not idiopathic, not insect nor drug in child	-	-	-	-	= 44.2%
	probability trigger was food given not not idiopathic, not insect nor drug in child	-	-	-	-	= 12.5%

Table 9: probabilities of trigger sub-groups

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

As stated in literature it is difficult to calculate the exact incidence rates of anaphylaxis due to difficulties with coding, diagnosis and reporting (Sampson 2005) [24] and actual rates remain unclear.

In the model the probability figures on anaphylaxis due to insect and idiopathic anaphylaxis (parameter 9 and 10) were estimated based on a one year study analyzing the Health Improvement Network (THIN) database on 2.3 million patients (age 10 to 79 years) who had been enrolled for at least one year with a GP in the UK (Gonzalez-Perez 2010)[5].

In the model the probabilities that anaphylaxis was due to drug were specified for adults and children (parameter 11) using the figures of a retrospective

study on emergency calls for allergic reactions within greater Manchester also in a one year period by the North West Ambulance Service in the UK (Capps et al. 2010)[25].

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 2009). This means that the probability of idiopathic 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. Next the probability of drug given not idiopathic or insect is calculated from 19/87 or 236/303, depending on whether child or adult. The probability of food given 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 ($r/\text{all anaphylaxis}=r/343$): idiopathic: 30.03%; insect: 13.41%; food: 44.21% (children), 12.51% (adults) and drug: 12.35% (children), 44.05% (adults).

Mortality

	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 HES 2010

Table 10: mortality from anaphylaxis

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 2008)[7]. This was based partly on a set of studies using a register of deaths due to anaphylaxis compiled by Pumphrey [26-28]. The number of anaphylaxis cases was estimated by figures for the period of 2009 to 2010 from the Department of Health Hospital Episode Statistics (www.hesonline.nhs.uk). As already stated in the section on incidence rates as it is difficult to diagnose and correctly code anaphylaxis, both of the reported figures are likely to be underestimates, 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%.

In order to estimate the effect of the adrenaline injectors, 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. Having calculated the probability with no AI, the effect of AIs can be applied, either with SC or with SS. As will be explained below, the parameter in the

model that estimates the effect of SC or SS is the proportion of correct use, which would be expected to be higher with SS 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.

Firstly, 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 since there is no trigger. Indeed, the register by Pumphrey and summarized by Soar et al [7] does contain this data for food, drug (oral and injected (although only oral used since 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. Actually all of these times were times to first cardiac arrest, but, given that they all 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 that died was similar to that in those avoided by either the emergency services (referred to as 'ambulance') or AI.

Therefore, firstly, the proportions dying in each of the categories reported by Soar et al (2.1-4.5, 4.6-9.9, 10-20 and >20 mins) was estimated, shown in Table 11.

	Parameter	Name of parameter in model	Distribution type	r in categories (2.1-4.5, 4.6-9.9, 10-20 and >20 mins)	Sources
14	Time to die, food	dtimediefood	Dirichlet	(0;0;9;50)	Soar et al 2008
15	Time to die, drug	dtimediedrug	Dirichlet	(0;2;4;7)	Soar et al 2008
16	Time to die, insect	dtimedieinsect	Dirichlet	(2;420;19)	Soar et al 2008

Table 11: model parameters of time to die for each trigger of anaphylaxis

'Drug' only included oral and not injected on the basis that injected would have been administered by 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 12.

Trigger	Categories			
	2.1-4.5 mins*	4.6-9.9 mins	10-20 mins	>20 mins
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 12: distribution of time to death by trigger of anaphylaxis

*mins = minutes

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

For example, about 62% of cases of anaphylaxis from any cause would still be alive up to 20 minutes, which means that they 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 less than 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 [29], 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 13.

	Parameter	Name of parameter in model	Distribution type	r in categories (<8, 8-18 and >18 mins*) 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
18	Ambulance response time, Category B	Dtime19B	Beta	2,559,126	2,322,793	NHS Information Centre 2010

Table 13: model parameters of ambulance response times

*mins = minutes

'<8 mins' is not reported for B and so it was assumed to be zero. This is unlikely to be a problem since the proportion of calls to anaphylaxis in category B is likely to be very small. Indeed the figures used were from Capps et al 2010 [25], where there were less than 10% in B (referred to as 'amber' in that study). 'Purple' and 'red' were assumed to be equivalent to A. <8mins was assumed to correspond to 4.6-9.9, assuming that response time would never be less than 4.6 minutes. 8-18 and 10-20 and >20 and >18 were assumed to be equivalent. These r and n values, used as inputs in the model, imply the following proportions, shown in Table 14.

Ambulance	Categories		
	<8 mins*	9-18 mins	>18 mins
Category A	0.743316	0.171142	0.085542
Category B	0	0.907651	0.092349
Any category	0.672829	0.240983	0.086187

Table 14: distribution of ambulance response times

*mins=minutes

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 only be saved by correct and timely use of AI. For example, all of those with a time to death less than 4.6 minutes would not be prevented whereas the proportion who would still

die in the 10-20 minutes category would be only those where the ambulance response time was in the >18 mins category. The formula is:

$$\text{Propnot}_{\text{amb}} = \text{propnot (2.1-4.5 mins)} + \text{propnot (4.6-9.9 mins)} + \text{propnot (10-20 mins)} + \text{propnot (>20 mins)}$$

Where $\text{propnot}_{\text{amb}}$ is the proportion of deaths that would occur due to anaphylaxis that are NOT prevented by ambulance, which depends on the response time distribution so that:

$$\begin{aligned} \text{Propnot}_{\text{amb}} = & \text{propdie (2.1-4.5 mins)} + ((1 - (\text{propresp}(<8 \text{ mins}) * 0.5)) * \text{propdie (4.6-9.9 mins)}) \\ & + ((1 - \text{propresp}(<8 \text{ mins}) - (\text{propresp}(8-18 \text{ mins}) * 0.5)) * \text{propdie (10-20 mins)}) \\ & + (1 - \text{propresp}(<8 \text{ mins}) - \text{propresp}(8-18 \text{ mins}) - (\text{propresp}(>18) * 0.5 \text{ mins})) \\ & * \text{propdie}(>20 \text{ mins}) \end{aligned}$$

Where propdie is the proportion who die in each time period, shown in Table 12 and propresp is the proportion who respond within that time period, shown in Table 14. It can be seen that $\text{propnot (2.1-4.5 mins)} = \text{propdie(2.1-4.5 mins)}$ 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.

From the data in the tables:

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

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 mins category. This implies that all those deaths not prevented by ambulance in the time less than 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 since this only applies to those who actually use the injector correctly: there is another parameter, which is the proportion who do this, which might be less than 100%. Indeed, in the Capps et al study, 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:

$$\text{Propnot}_{\text{amb+AI}} = \text{propnot}_{\text{amb}} (2.1-4.5) + (\text{propnot}_{\text{amb}} (4.6-9.9) * P_{\text{correct}} * 0.5) + (\text{propnot}_{\text{amb}} (10-20) * P_{\text{correct}}) + (\text{propnot} (>20) * P_{\text{correct}})$$

i.e. the proportion of deaths prevented by AI in each time period is the probability of correct use, P_{correct} (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:

$$P_{\text{propnot}_{\text{amb+AI}}} = 0.087852$$

i.e. about 9% of deaths are prevented by both ambulance and AI use. This is therefore the proportion of the anaphylaxis mortality rate (without any intervention), which die given current service ambulance service provision and current AI use. Therefore, to calculate the overall (no intervention) mortality rate, P_{death} , use:

$$P_{\text{death}} = N_{\text{no intervention}} / N_{\text{anaphylaxis}} \quad (1)$$

$$N_{\text{intervention}} = p_{\text{intervention}} * N_{\text{no intervention}} \quad (2)$$

Where $N_{\text{intervention}}$ is the number of deaths with current service and AI use, which is 20 (see Table 10); $p_{\text{intervention}}$ is the proportion of deaths not saved, which was calculated to be 0.087852 and $N_{\text{no intervention}}$ is the number of deaths that would have occurred and $N_{\text{anaphylaxis}}$ is the number of cases of anaphylaxis, which is 3517 (see above).

Substituting (2) into (1) gives:

$$P_{\text{death}} = N_{\text{intervention}} / \text{Prop}_{\text{not}_{\text{amb+AI}}} / N_{\text{anaphylaxis}} \\ = 20 / 0.087852 / 3517 \\ = 0.064729$$

i.e. the probability of dying from anaphylaxis without any treatment would be about 6%, which would result in $3517 * 0.064729 =$ about 228 deaths per year. Therefore, we can now fulfill the aim of this section and calculate the probability of dying with ambulance and no AI, which is:

$$P_{\text{death no AI}} = \text{Prop}_{\text{not}_{\text{amb}}} * P_{\text{death}} \\ = 0.129472 * 0.064729 \\ = 0.008381, \text{ which would result in } 3517 * 0.008381 = \text{about } 29$$

deaths per year.

$P_{\text{death no AI}}$ is the probability of death used in the model for no injector use. This means that $P_{\text{death AI}}$ is the probability of death with correct AI use (recall that those deaths below 4.6 minutes would not be prevented even with correct use), which can be calculated by assuming that the proportion given AI is 100%:

$$P_{\text{death AI 100\%}} = 0.00389 * 0.064729 \\ = 0.000252, \text{ which would result in } 3517 * 0.000252 = \text{about } 1$$

death per year.

This is because the only deaths not prevented by 100% correct AI use is those that occur within 4.5 minutes. This means that, whereas current AI use (44%) saves about 9 deaths per year, if AI use was 100% correct, there would only be about 1 death per year, saving an extra 8 deaths per year.

In the model, P_{death} is calculated by using P_{correct} from Capps et al 2010 [25] of 53/116 (about 44%) (see Table 15).

	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 n= table 3 page 655 at any time r=before ambulance arrived

Table 15: model parameter for current probability of correct use of AI used only to calculate underlying probability of death due to anaphylaxis, P_{death} (see text)

This is not the value used to estimate the probability of correct use in the model i.e. during the cohort simulation since in Capps et al were also presented separate values for child (<15 years) and adult (shown with the value for SS in Table 16).

	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 n= table 3 page 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 n= table 3 page 655 r=before ambulance arrived (adult)

Table 16: model parameters for probability of correct use of AI with SC

The probability of using an AI given SC (parameters 20 and 21) was based on the figures of use of AIs before arrival of the North West Ambulance Service (Capps et al. 2010) and the total number of patients who got 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. implies not all patients who have the symptoms of an anaphylactic reaction need/received an adrenaline injection for treatment.

It is expected that the compliance of who patients received education (in SS) will increase (parameter 22). Compliance of adrenaline injectors is mainly dependent on the knowledge of how to use it in a correct way, as well as the will to ensure 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% use was assumed, although recall that this still means that those with a very short time to die (<4.6 mins category from Soar et al) will still die (see Table 17). This makes the estimate more conservative.

	Parameter	Name parameter in model	Distribution type	n	r	Sources
22	probability use injector correctly with SS	dpinjectorSS	Triangular	1		assumption

Table 17: model parameters for probability of correct use of AI with SS

Idiopathic treatment

Estimates to calculate probability of remission came from an observational study by Krasnick et al 1996, which was used because it was the only study that could be found that had any time to event data in order to estimate the probability of remission. It was presented as time years of follow-up and years in remission from which time to remission could be calculated by subtraction. Table 18 shows the data extracted for frequent and infrequent recurrence categories.

Frequent recurrence			Infrequent recurrence		
years follow-up	years in remission	time to remission	years 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	NR*	6	6	0	6
18	NR*	18	9	1	8
7	NR*	7	6	NR	6
9	NR*	9			
5	NR*	5			

Table 18: data (years follow-up and in remission) extracted from Krasnick et al 1996, used to calculate time to remission

From this data the median of time to remission was calculated, which was then used to inform the estimates 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 (see Table 19)

	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
24	Median time to remission in infrequent idiopathic	dmedianinfreq	Triangular	1	1.5	2	based on data from Krasnick et al 1996

Table 19: parameters to estimate probability of remission

It was assumed that the rate of recurrence in 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 toward either SC or SS. The proportion of frequent anaphylaxis (0.5) was also taken from the study by Krasnick et al [30], which use the same definition of frequent as the guideline, shown in Table 20.

	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

Table 20: proportion of idiopathic patients that have frequent recurrence

Venom immunotherapy (VIT)

	Parameter	Name of parameter in model	Distribution type	Base case	Range Min	Range Max	Sources
26	Effectiveness of VIT	dpeffectVIT	Triangular	0.75	0.85	0.95	Based on Krishna 2010
27	Dropout	dropout	Triangular	0.1	0.2	0.3	Based on Goldberg 2000
28	Uptake of VIT	duptakeVIT	Triangular	0.4	0.6	0.8	Based on Cox 2011

Table 21: VIT parameters

VIT is indicated for patients who had a history of severe systemic reaction to a sting (Golden 2005). The effectiveness of VIT (parameter 26) is estimated to be 85%; this is based on several studies who report a range of effectiveness of 75 to 95% (Krishna 2010) [31]. 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 with access to adrenaline and other emergency care (based on Cox 2010)[14]. As VIT is time-consuming both in 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 the immunotherapy for three years (parameter 27). This figure is based on the a finding of Goldberg et al who reported a dropout rate of 40% in a study evaluating the attitudes of patients with insect venom allergy regarding after-sting behavior and proper administration of epinephrine in Israel (Goldberg 2000). We assumed that in the UK, ten years later the dropout rate of VIT will be much lower (about 20%) due to better care and less adverse events. Also, because of knowledge of these problems and that, depending on the results of skin and anti IgE testing, not everyone is eligible (as low as 65% according to Cox et al , it was conservatively estimated that uptake would be about 60% (parameter 28).

Health valuation estimation

	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	based on Voordouw 2010
30	Duration of recurrence	ddurationrecur	Uniform	1	n/a	9	based on Neuner et al 2003
31	Utility factor with SS	duSSimprove	Triangular	0	0.25	0.5	Assumption based on EO
32	Utility factor with AI	duAIimprove	Triangular	0	0.25	0.5	Assumption based on EO

Table 22: utilities

For the calculation of Quality Adjusted Life Years of the NICE reference case [9] 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 [32]. 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 2010 [33] was used. This case-control study 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 (Voordouw 2010). 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 controls, $p < 0.05$) (parameter 29).

We presumed that the impact of an anaphylaxis will be very short, but profound. The estimation of mean duration of having recurrence of anaphylaxis (parameter 30) was based on the finding that the mean loss of about 9 whole quality adjusted life days for severe allergic reaction due to penicillin, which is equivalent to utility decrement of the whole of the age dependent utility for 1 to 9 days, reported in another CEA (Neuer et al. 2003). Unfortunately, this value was not 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 (www.hesonline.nhs.uk) 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). Therefore, in the absence of any evidence as to the extent of this effect, ranges of 0 to 0.5 for a factor to be multiplied by a utility increment equal to the decrement due to anaphylaxis, were chosen for each of SS and AI (parameter 32). 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).

Discount rate

The discount rate for costs and benefits was 3.5% in accordance with NICE methods guidance [9].

General model assumptions

We assumed that 50 % of the population consisted of males, which is based on the 2010 Department of Health Hospital Episode Statistics (www.hesonline.nhs.uk). 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 Standard Care (SC) there is either no referral to SS or referral only to GP after anaphylaxis and that SS essentially consisted of SC plus referral to specialist service 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 only gets two sessions with specialist service (SS) 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 SS and from only mortality rate reductions with AI. We assumed that historic recurrence and mortality rates are due to standard care (SC) only, given the likely low rate of referral to SS: in one study the referral rate was zero [3]. Finally, we expected that 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 SS being cost effective.

Further assumptions are explained in each of the section on Model parameters below.

Time horizon

The time horizon was lifetime in accordance with NICE methods guidance [9].

6.2.2 Results

Base case results

An arbitrary age of 30 was chosen for the base case and the **Table 23** and **Figure 3** show the results of the model run probabilistically (10,000 simulations):

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (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

Table 23: base case results (probabilistic)

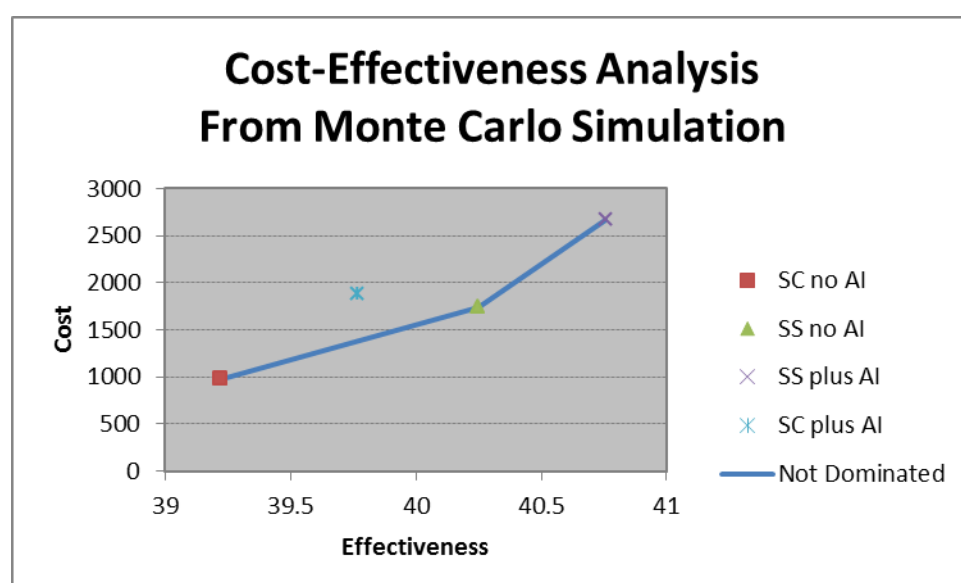


Figure 3: base case results (probabilistic)

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 greater than £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:

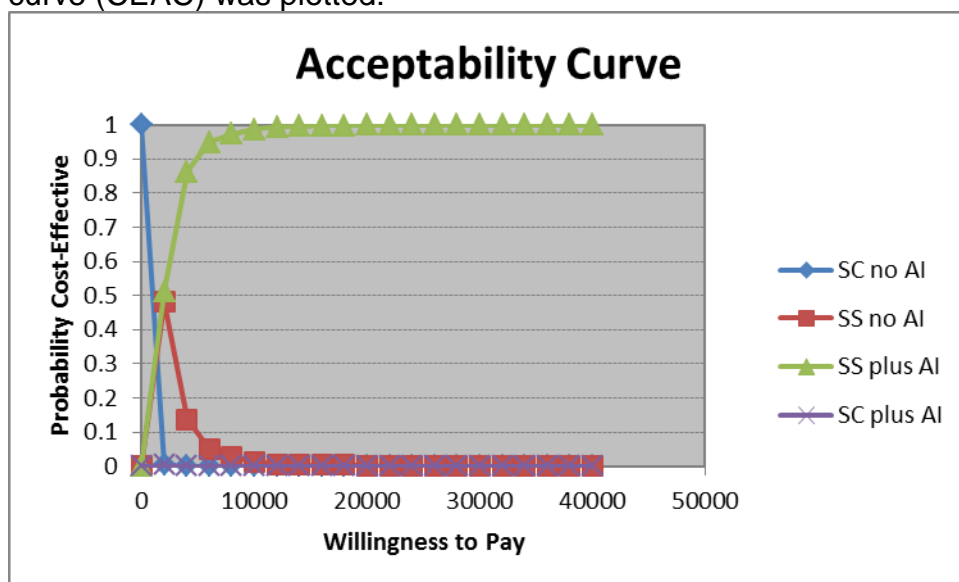


Figure 4: CEAC: base case

Figure 4 shows that at a threshold above about £2,000 per QALY, SS with AI is could be most likely to be cost effective and below this SS without AI would be most likely.

The next table shows the results of the deterministic (parameters at expected values) analysis:

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (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

Table 24: base case results (deterministic)

It can easily be seen that there is virtually no difference between the results indicating that the expected cost and QALYs 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.

Sensitivity analysis

Table 25 Error! Reference source not found. shows the results for age 5.

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
SC no AI	1137.78		61.05		18.64	
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 25: results at age 5 (base case age 30)

It shows essentially very similar results to age 30, except that SC plus AI was extendedly dominated (ICER to move from SC no AI greater than to move from SC plus AI to SS no AI).

Error! Reference source not found. shows the effect of varying the time horizon instead using a lifetime.

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
Start age 30						
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	37207.02
Start age 5						
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	26689.05

Table 26: time horizon 2 yrs (base case lifetime)

What it shows is that, as the time horizon decreases, SS plus AI becomes less likely to be cost effective. Indeed, threshold analysis (see next paragraph) reveals that, starting at age 30, 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 to 90, base case: 30)
- Probability trigger was drug
- 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 SS (up to 10 times base case for all in multi-way sensitivity analysis)
- Cost of specialist service (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 two years)
- Proportion frequent idiopathic
- Probability of remission, either in frequent or infrequent
- Cost per mg of prednisolone (up to £1, base case: £0.02)
- Cost of VIT (initial or maintenance) (up to £200)
- Effectiveness of VIT (0 to 1, base case: 0.85)
- Probability of dying from anaphylaxis with no intervention
- Utility improvement factor for SS (0 to 0.5, base case: 0.25)
- Utility improvement factor for AI (0 to 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: 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, three years and, for children, 2 years (base case: lifetime)

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 at relatively extreme values of a small number of parameters.

6.2.3 Discussion

Key results

The analysis 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 adrenaline injector (AI)?

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

- 1) SC (standard care) plus no AI (adrenaline injector)
- 2) SC plus AI
- 3) SS (specialist service) plus no AI
- 4) SS plus AI

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

A Markov model was constructed to model the possibility of recurrence over a lifetime in each of the sub-groups by cause of anaphylaxis, insect, food, drug and idiopathic. It modeled the effect of SS 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 modeled as having an effect only on mortality due to recurrence. The results showed that, in the base case of a lifetime horizon, 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) 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 specialist service could cause a change to standard care. 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 due to prescription of an injector) could cause a change to specialist service with no injector.

Generalisability

The 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 standard care, 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 specialist service, 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.

Strengths

Firstly, the methods were those recommended in the NICE guidance [9], 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.

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

Thirdly, 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.

Fourthly, 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 SS had never been estimated before. One study [34] 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

Although validation by expert opinion did occur, several assumptions were made and, although parameter values were obtained, many did rely on EO. 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 [5] to be about 30%, but this did not differentiate by age. Two other UK studies were found that did differentiate cause by age [3, 25, 35], but it was not clear how many had idiopathic, although the proportion with 'aetiology not recorded' was about 34% (children 27% and adults 35%) in one study [35] and 'allergen not documented' 40% for both adults and children in the other [25]. Also,

variation of this proportion by itself had no effect on the cost effective strategy.

Secondly, for recurrence, only cost of hospital treatment for anaphylaxis was included, but this was conservative in relation to the effect of rate reduction by specialist service and even if reduced to zero, it would not change which strategy was cost effective. Cost of specialist service might have been too low if any capital investment was required, but even raising it to the equivalent of about fifty sessions had no effect. The only cost parameter change that had a threshold was that of the injectors, which were costed using the BNF 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 specialist service without injector.

Thirdly, 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 would prescription of AI not be cost effective. Fourthly, there was no direct evidence for the influence of AI or SS on utility, but even a factor of 0 for SS or AI had no effect on which strategy was cost effective.

Fifthly, 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 SS. 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 SS. Finally, the evidence used for effectiveness of specialist service 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, again variation in most parameters e.g. this parameter or 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 [\[11\]](#), 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 SS, but, on the other hand it would also decrease the cost of SS relative to SC due to 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 standard care cost effective.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Not applicable

8. DISCUSSION

Not applicable

9. CONCLUSIONS

Not applicable

10. REFERENCES

Please use the Vancouver format (i.e. consecutive numbering throughout the main text with up to six authors quoted in full followed by et al in the reference list. There should not be any references in the executive summary). For example:

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11. APPENDICES

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 & history taking search)

The clinical assessment search was conducted in February 2011.

OvidSP Medline <1948-2011/2/wk 1>, searched 16/02/2011

- 1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83258)
- 2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15288)
- 3 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (24149)
- 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 (105987)
- 7 exp Emergency Treatment/ (80137)
- 8 (Accident adj2 emergency).ti,ab,ot,hw. (3474)
- 9 exp Emergency Medical Services/ (75543)
- 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. (115106)
- 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/ (30977)
- 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 (213695)

- 21 Physical Examination/ (25045)
- 22 ((clinical\$ or physical\$) adj2 (assess\$ or exam\$ or test\$ or history or histories)).ti,ab,ot,hw. (166918)
- 23 exp medical history taking/ or cornell medical index/ (16109)
- 24 ((Medical\$ or patient\$) adj2 (histories or history)).ti,ab,ot,hw. (38080)
- 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. (65478)
- 27 exp skin tests/ (50471)
- 28 (allerg\$ adj1 (test\$ or investigat\$)).ti,ab,ot,hw. (1982)
- 29 (Sensitivit\$ adj1 (test\$ or investigat\$)).ti,ab,ot,hw. (80112)
- 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. (40005)
- 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. (10447)
- 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 (402839)
- 48 6 and 20 and 47 (271)
- 49 animals/ not (animals/ and humans/) (3403655)
- 50 48 not 49 (268)

OvidSP Medline In-Process Citations <up to 2011/2/15> and Medline Daily Update <up to 2011/2/15>, searched 16/02/2011.

- 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 Fluorezymeimmunoassay\$.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 (12625)

48 6 and 20 and 47 (4)

49 animals/ not (animals/ and humans/) (2774)

50 48 not 49 (4)

OvidSP Embase <up to 2011/wk 6>, searched 17/02/2011.

1 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (87798)

2 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18305)

3 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32758)

4 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (39238)

- 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 (136815)
- 8 animal/ or animal experiment/ (3045231)
- 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. (4666017)
- 10 or/8-9 (4666017)
- 11 exp human/ or human experiment/ (12216815)
- 12 10 not (10 and 11) (3748300)
- 13 7 not 12 (122765)
- 14 EMERGENCY/ (24427)
- 15 emergency treatment/ or evidence based emergency medicine/ or first aid/ or pediatric advanced life support/ (20946)
- 16 emergency care/ (10408)
- 17 Emergency-Medicine/ (16466)
- 18 Emergency-Health-Service/ (50147)
- 19 Emergency-Patient/ (545)
- 20 Emergency-Ward/ (31998)
- 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. (146375)
- 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. (10473)
- 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 (184896)
- 31 clinical assessment/ (33978)
- 32 Physical Examination/ (94953)
- 33 Medical-History/ or anamnesis/ (104176)

- 34 Allergy-Test/ (2167)
- 35 ((clinical\$ or physical\$) adj2 (assess\$ or exam\$ or test\$ or history or histories)).ti,ab,ot,hw. (320112)
- 36 ((Medical\$ or patient\$) adj2 (histories or history)).ti,ab,ot,hw. (34556)
- 37 Anamnesis.ti,ab,ot,hw. (103947)
- 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. (80772)
- 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. (38783)
- 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. (12367)
- 46 ((patch or percutaneous\$ or epicutaneous\$) adj1 (test\$ or investigat\$)).ti,ab,ot,hw. (14561)
- 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 (556805)
- 59 13 and 30 and 58 (621)
- 60 animal/ or animal experiment/ (3045231)
- 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. (4666017)
- 62 or/60-61 (4666017)
- 63 exp human/ or human experiment/ (12216815)

- 64 62 not (62 and 63) (3748300)
 65 59 not 64 (621)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 1:2011
 and Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
 Issue 1:2011, searched 18/02/2011.

- 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 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) 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) 10188

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 11235

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) 18252

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) 21882

60 (#15 AND #30 AND #59) 6

[CDSR search retrieved 0 records. CENTRAL search retrieved 6 records.]

Database of Abstracts of Reviews of Effects (DARE) (Internet) <2000-2011/02/17>, Health Technology Assessment (HTA) (Internet) <2000-2011/02/17>, and NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/02/17> via <http://www.crd.york.ac.uk/crdweb/>. Searched 18/02/2011.

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* 10264

34 #31 or #32 or #33 11899

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*) 15013

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*) 10981

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 20628

44 #35 and #43 386

[DARE search retrieved 205 records. NHS EED search retrieved 165 records. HTA search retrieved 16 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

32 503 #31 and #30

Databases=SCI-EXPANDED Timespan=All Years

31 1,391 #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 challenge 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 1,538 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 3,155 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 Fluorezymeimmunoassay*)

Databases=SCI-EXPANDED Timespan=All Years

20 4,189 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 3,039 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 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

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011

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 (161809)

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*)
(91791)

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) (88383)

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

S16 (MH "Physical Examination+") OR (MH "Skin Tests+") (45744)

S15 (MH "Clinical Assessment Tools+") (66572)

S14 s9 and s13 (379)

S13 s10 or s11 or s12 (105090)

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*)) (99683)

S11 (MH "Emergency Medical Services+") (40158)

S10 (MH "Emergencies") (3245)

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+") (20402)

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

The auto-injectors search was conducted in February/March 2011.

OvidSP Medline <1948-2011/2/wk 3>, searched 24/02/2011.

- 1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (84731)
- 2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15506)
- 3 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (24636)
- 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 (107806)
- 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/) (3452597)
- 14 12 not 13 (333)

OvidSP Medline In-Process Citations <up to 2001/02/23> and OvidSP Medline Daily Update <up to 2001/02/23>, searched 24/02/2011.

- 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)

OvidSP Embase <1980-2011/wk 10>, searched 16/03/2011.

- 1 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88290)
- 2 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18423)
- 3 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32909)
- 4 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (39414)
- 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 (137588)
- 8 animal/ or animal experiment/ (3059048)
- 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. (4688188)
- 10 or/8-9 (4688188)
- 11 exp human/ or human experiment/ (12277839)
- 12 10 not (10 and 11) (3764868)
- 13 7 not 12 (123461)
- 14 intramuscular drug administration/ (54836)
- 15 adrenalin/ (75165)
- 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 and Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011, searched 16/03/2011.

- 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 ((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

[CDSR search retrieved 2 records. CENTRAL search retrieved 15 records.]

Database of Abstracts of Reviews of Effects (DARE) (Internet) <2000-2011/03/16>, Health Technology Assessment (HTA) (Internet) <2000-2011/03/16>, and NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/03/16> via <http://www.crd.york.ac.uk/crdweb/>. Searched 16/03/2011.

- 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* NEAR 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

[DARE searched retrieved 3 records. NHS EED searched retrieved 2 records. HTA searched retrieved 0 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

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 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

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011

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+") (20402)

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

The referral search was conducted in February/March 2011.

OvidSP Medline <1948-2011/03/wk 1>, searched 16/03/2011

- 1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (84975)
- 2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15556)
- 3 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (24706)
- 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 (108132)
- 7 "referral and consultation"/ or gatekeeping/ (44777)
- 8 (Refer\$ or consultation\$ or Gatekeep\$ or gatekeep\$).ti,ab,ot,hw. (579743)
- 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. (799644)
- 11 Outpatient Clinics, Hospital/ (13094)
- 12 (Allergist\$ or aftercare or after-care).ti,ab,ot,hw. (8709)
- 13 aftercare/ (6002)
- 14 (Allerg\$ clinic\$ or Specialist clinic\$).ti,ab,ot,hw. (1160)
- 15 or/7-14 (1332348)
- 16 6 and 15 (6587)
- 17 animals/ not (animals/ and humans/) (3464943)
- 18 16 not 17 (6367)
- 19 exp Emergency Treatment/ (81416)
- 20 (Accident adj2 emergency).ti,ab,ot,hw. (3508)
- 21 exp Emergency Medical Services/ (76776)
- 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. (116473)
- 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. (829)
- 24 (Accident adj2 emergency).ti,ab,ot,hw. (3508)
- 25 Triage\$.ti,ab,ot,hw. (9975)

- 26 First aid\$.ti,ab,ot,hw. (8343)
- 27 (First response\$ or first respond\$).ti,ab,ot,hw. (1567)
- 28 (Medical adj2 urgen\$).ti,ab,ot,hw. (431)
- 29 Emergencies/ (31418)
- 30 (postepisod\$ or postadmission\$ or postadmit\$ or postreaction\$ or postevent\$ or postincident\$).ti,ab,ot,hw. (380)
- 31 (post adj (episod\$ or admission\$ or admit\$ or reaction\$ or event\$ or incident\$)).ti,ab,ot,hw. (545)
- 32 or/19-31 (216773)
- 33 18 and 32 (237)

OvidSP Medline In-Process Citations <up to 2011/03/15> and OvidSP Medline Daily Update <up to 2011/03/15>, searched 16/03/2011

- 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. (26867)
- 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. (22520)
- 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 (47842)
- 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)

OvidSP Embase <1980-2011/wk 10>, searched 17/03/2011

- 1 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88290)
- 2 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18423)
- 3 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32909)
- 4 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (39414)
- 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 (137588)
- 8 Outpatient-Department/ or Patient Referral/ or exp Consultation/ or exp Aftercare/ or Outpatient/ (647761)
- 9 (Second opinion\$ or 2nd opinion\$).mp. (1321)
- 10 (Refer\$ or consultation\$ or Gatekeep\$ or gatekeep\$).mp. (587999)
- 11 (followup\$ or follow-up\$ or outpatient\$ or out-patient\$).mp. (906230)
- 12 (Allergist\$ or aftercare or after-care).mp. (8120)
- 13 (Allerg\$ clinic\$ or Specialist clinic\$).mp. (1752)
- 14 or/8-13 (1441363)

- 15 emergency treatment/ or evidence based emergency medicine/ or first aid/ or pediatric advanced life support/ (21042)
- 16 emergency care/ or EMERGENCY/ or Emergency-Medicine/ or Emergency-Health-Service/ (97139)
- 17 Emergency-Patient/ or Emergency-Ward/ (32763)
- 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. (168221)
- 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. (20469)
- 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 (193229)
- 26 7 and 15 and 25 (553)
- 27 animal/ or animal experiment/ (3059048)
- 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. (4688188)
- 29 27 or 28 (4688188)
- 30 exp human/ or human experiment/ (12277839)
- 31 29 not (29 and 30) (3764868)
- 32 26 not 31 (546)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 3:2011 and Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011, searched 17/03/2011.

- | | | |
|----|--|-----|
| 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 37266

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 88074

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) 118191

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) 10192

41 (#15 AND #25 AND #40) 4

[CDSR search retrieved 0 records. CENTRAL search retrieved 2 records.]

Database of Abstracts of Reviews of Effects (DARE) (Internet) <2000-2011/02/17>, Health Technology Assessment (HTA) (Internet) <2000-2011/02/17> and NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/02/17> via <http://www.crd.york.ac.uk/crdweb/>. Searched 17/03/2011

- 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* 14313
- 32 (Second NEAR opinion*) OR (2nd NEAR opinion*) 70
- 33 (followup* OR follow-up* OR outpatient* OR out-patient*) 13004
- 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 20112
- 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

[DARE search retrieved 42 records. NHS EED search retrieved 49 records.
HTA search retrieved 2 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

21 1,033 #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 2,720 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 3,039 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 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

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011.

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

S20 s14 or s15 or s16 or s17 or s18 or s19 (579982)

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*)) (579982)

S18 (MH "After Care") (4003)

S17 (MH "Outpatient Service") (2648)

S16 (MH "Outpatients") (25019)

S15 (MH "Gatekeeping") (187)

S14 (MH "Referral and Consultation+") (12876)

S13 s9 and s12 (379)

S12 s10 or s11 (105090)

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*)) (99683)

S10 (MH "Emergencies") or (MH "Emergency Medical Services+") (42909)

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+") (20402)

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.

OvidSP Medline <1948-2011/02/wk 1>, searched 11/02/2011

- 1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83258)
- 2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15288)
- 3 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (24149)
- 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 (105987)
- 7 Recurrence/ (135626)
- 8 (Recrudescen\$ or recur\$ or repeat\$ or re-occur\$ or reoccur\$ or subsequent\$ or repetition\$ or repeat\$).ti,ab,ot,hw. (1090520)
- 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 (1094231)
- 11 risk/ or risk assessment/ or risk factors/ (597934)
- 12 (risk or risks or likelihood\$).ti,ab,ot,hw. (1200489)
- 13 or/11-12 (1200489)
- 14 10 and 13 (143543)
- 15 6 and 14 (1168)
- 16 animals/ not (animals/ and humans/) (3403655)
- 17 15 not 16 (1130)

OvidSP Medline In-Process Citations <up to 2011/02/10> and OvidSP Medline Daily Update <up to 2011/02/10>, searched 11/02/2011.

- 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. (47641)
- 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 (47873)
- 11 risk/ or risk assessment/ or risk factors/ (737)
- 12 (risk or risks or likelihood\$).ti,ab,ot,hw. (46261)
- 13 or/11-12 (46261)
- 14 10 and 13 (5026)
- 15 6 and 14 (10)
- 16 animals/ not (animals/ and humans/) (1531)
- 17 15 not 16 (10)

OvidSP Embase <1980-2011/wk 6>, searched 14/02/2011.

- 1 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (87798)
- 2 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18305)
- 3 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32758)
- 4 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (39238)
- 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 (136815)
- 8 Recurrent-Disease/ (106106)
- 9 (Recrudescen\$ or recur\$ or repeat\$ or re-occur\$ or reoccur\$ or subsequent\$ or repetition\$ or repeat\$).ti,ab,ot,hw. (1256741)
- 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 (1261628)

- 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/ (864642)
- 13 (risk or risks or likelihood\$.ti,ab,ot,hw. (1580892)
- 14 or/12-13 (1580892)
- 15 11 and 14 (185931)
- 16 Recurrence-Risk/ (20568)
- 17 15 or 16 (185931)
- 18 7 and 17 (2354)
- 19 animal/ or animal experiment/ (3045231)
- 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. (4666017)
- 21 or/19-20 (4666017)
- 22 exp human/ or human experiment/ (12216815)
- 23 21 not (21 and 22) (3748300)
- 24 18 not 23 (2304)

Cochrane Database of Systematic Reviews (CDSR) (Internet) Issue 1:2011 and Cochrane Central Register of Controlled Trials (CENTRAL) (Internet) Issue 1:2011, searched 17/02/2011.

- 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 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) 2810
 16 MeSH descriptor Recurrence, this term only 10438
 17 (recrudescen* OR recur* OR repeat* OR re-occur* OR subsequent* OR repetition* OR repeat*):ti,ab,kw 59339
 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) 59572
 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 15176
 23 (risk or risks OR likelihood*):ti,ab,kw 66166
 24 (#20 OR #21 OR #22 OR #23) 66166
 25 (#15 AND #19 AND #24) 59
 [CDSR search retrieved 2 records. CENTRAL search retrieved 57 records.]

Database of Abstracts of Reviews of Effects (DARE) (Internet) <2000-2011/02/17>, Health Technology Assessment (HTA) (Internet) <2000-2011/02/17>, and NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/02/17> via <http://www.crd.york.ac.uk/crdweb/>. Searched 17/02/2011.

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*)	13669
71	#69 or #70	15477
72	#65 AND #71	3369
73	#59 AND #72	200

[DARE search retrieved 129 records. NHS EED search retrieved 61 records. HTA search retrieved 10 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

12 3,367 #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 3,702 #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 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

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011.

S17 s9 and s16 Limiters - Exclude MEDLINE records (196)
 S16 s12 and s15 (22108)
 S15 s13 or s14 (250339)
 S14 TX (risk or risks or likelihood*) (250339)
 S13 (MH "Risk Assessment") OR (MH "Risk Factors") (64318)
 S12 s10 or s11 (97852)
 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*)) (97852)
 S10 (MH "Recurrence") (12583)
 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+") (20402)

Economic search

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

OvidSP MEDLINE <1948-2011/03/wk 2> , searched 17/03/2011.

- 1 economics/ (25965)
- 2 exp "costs and cost analysis"/ (154360)
- 3 economics, dental/ (1814)

4 exp "economics, hospital"/ (17009)
 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. (327719)
 9 (expenditure\$ not energy).ti,ab. (13900)
 10 (value adj1 money).ti,ab. (18)
 11 budget\$.ti,ab. (14162)
 12 or/1-11 (439089)
 13 ((energy or oxygen) adj cost).ti,ab. (2243)
 14 (metabolic adj cost).ti,ab. (578)
 15 ((energy or oxygen) adj expenditure).ti,ab. (12794)
 16 or/13-15 (15012)
 17 12 not 16 (435668)
 18 letter.pt. (707514)
 19 editorial.pt. (270646)
 20 historical article.pt. (271900)
 21 or/18-20 (1237508)
 22 17 not 21 (411802)
 23 animals/ not (animals/ and humans/) (3467241)
 24 22 not 23 (388655)
 25 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or
 hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or
 eosinophilic esophagitis/ (85022)
 26 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis,
 allergic bronchopulmonary/ or latex hypersensitivity/ (15572)
 27 (Anaphyla\$ or pseudoanaphyla\$.ti,ab,ot,hw. (24719)
 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 (108202)
 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 13.1.11]. Available from:
http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

OvidSP Medline In-Process Citations <up to 2011/03/16> and OvidSP Medline Daily Update < up to 2011/03/16>, searched 17/03/2011]

- 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. (21859)
- 9 (expenditure\$ not energy).ti,ab. (657)
- 10 (value adj1 money).ti,ab. (2)
- 11 budget\$.ti,ab. (1252)
- 12 or/1-11 (23138)
- 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 (22934)
- 18 letter.pt. (15937)
- 19 editorial.pt. (9720)
- 20 historical article.pt. (115)
- 21 or/18-20 (25758)
- 22 17 not 21 (22640)
- 23 animals/ not (animals/ and humans/) (1312)
- 24 22 not 23 (22627)
- 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 13.1.11]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

OvidSP Embase <1980-2011/wk 10>, searched 17/03/2011.

- 1 health-economics/ (29979)
- 2 exp economic-evaluation/ (164685)
- 3 exp health-care-cost/ (158213)
- 4 exp pharmacoeconomics/ (135242)
- 5 or/1-4 (379306)
- 6 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$.ti,ab. (422362)
- 7 (expenditure\$ not energy).ti,ab. (16881)
- 8 (value adj2 money).ti,ab. (884)
- 9 budget\$.ti,ab. (17911)
- 10 or/6-9 (440596)
- 11 5 or 10 (666254)
- 12 letter.pt. (721412)
- 13 editorial.pt. (367270)
- 14 note.pt. (436494)
- 15 or/12-14 (1525176)
- 16 11 not 15 (596935)
- 17 (metabolic adj cost).ti,ab. (638)
- 18 ((energy or oxygen) adj cost).ti,ab. (2507)
- 19 ((energy or oxygen) adj expenditure).ti,ab. (14885)
- 20 or/17-19 (17369)
- 21 16 not 20 (593002)
- 22 animal/ or animal experiment/ (3059048)
- 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. (4688188)
- 24 or/22-23 (4688188)
- 25 exp human/ or human experiment/ (12277839)
- 26 24 not (24 and 25) (3764868)
- 27 21 not 26 (567207)
- 28 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88290)
- 29 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18423)
- 30 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32909)

- 31 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (39414)
- 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 (137588)
- 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 17.3.11]. Available from: <http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase>]

Health Technology Assessment (HTA) (Internet) <2000-2011/03/16> via <http://www.crd.york.ac.uk/crdweb/>. Searched 17/03/2011.

- 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 (econom* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmacoeconomic* OR budget*) 35538

32 (expenditure* NOT energy) 738

33 (value NEAR money) 204

34 #31 or #32 or #33 35555

35 #30 and #34 396

[HTA search retrieved 28 records.]

NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/03/16> via <http://www.crd.york.ac.uk/crdweb/>. Searched 17/03/2011.

- 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

[NHS EED search retrieved 299 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

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 13.1.11]. Available from:
http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011

S13 s9 and s12 Limiters - Exclude MEDLINE records (651)

S12 s10 not s11 (158410)

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*)) (159067)

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+") (20402)

Appendix 2: Quality and strength of evidence of included studies

The criteria used in this checklist are adapted from: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. *Annals of Internal Medicine* 144: 427–37.

Cianferoni 2004 Cianferoni, A., E. Novembre, et al. (2004). "Anaphylaxis: a 7-year follow-up survey of 46 children." <i>Annals of Allergy Asthma & Immunology</i> 92(4): 464-468.	
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 (that is, 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 Decker, K. W., M. F. Bellolio, et al. (2008). "Recurrent anaphylaxis events in patients presenting to the emergency department over a 10-year period." <i>Annals of Emergency Medicine</i> 51(4): 214.	
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 which 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 (that is, 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

Mehl, A., U. Wahn, et al. (2005). "Anaphylactic reactions in children--a questionnaire-based survey in Germany." *Allergy* 60(11): 1440-1445.

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 which 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 (that is, 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	
Múgica Garcia, M., M. Tejedor Alonso, et al. (2010). A study of the recurrence of anaphylaxis. <i>Allergy: European Journal of Allergy and Clinical Immunology</i> . Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom. Conference Publication: (var.pagings). 65 (pp 587), 2010. Date of Publication: June 2010.	
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, gender, weight and ethnicity.
2. Loss to follow-up is unrelated to key characteristics (that is, 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	
Mullins, R. J. (2003). "Anaphylaxis: risk factors for recurrence." <i>Clinical & Experimental Allergy</i> 33(8): 1033-1040.	
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 (that is, 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.

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. *Annals of Allergy Asthma & Immunology*. 2004 Apr;92(4):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. *Annals of Emergency Medicine*. 2008 Apr;51(4):214.
3. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children--a questionnaire-based survey in Germany. *Allergy*. 2005 Nov;60(11):1440-5.
4. Múgica Garcia M, Tejedor Alonso M, Rojas Perez Ezquerra P, Moro Moro M, Vila Albelda C, Rosado Ingelmo A, et al., editors. A study of the recurrence of anaphylaxis. *Allergy: European Journal of Allergy and Clinical Immunology Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom Conference Start: 20100605 Conference End: 20100609 Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom Conference Start: 20100605 Conference End: 20100609 Conference Publication: (varpagings) 65 (pp 587), 2010 Date of Publication: June 2010; 2010.*
5. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy*. 2003 Aug;33(8):1033-40.

List of studies with potential relevance for the background of the guideline

1. Abraham D, Grammer L. Idiopathic anaphylaxis. *Immunology and Allergy Clinics of North America*. 2001 Nov;21(4):783-+.
2. Alrasbi M, Sheikh A. Comparison of international guidelines for the emergency medical management of anaphylaxis. *Allergy*. 2007 Aug;62(8):838-41.
3. Bonifazi F, Jutel M, Bilo BM, Birnbaum J, Muller U. Hypersensitivity EIGoIV. Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. *ALLERGY*. 2005 Dec;60(12):1459-70.
4. Choo K, Sheikh A. Action plans for the long-term management of anaphylaxis: Systematic review of effectiveness. *CLINICAL AND EXPERIMENTAL ALLERGY*. 2007;37(7):1090-4.
5. Ellis AK, Day JH. Diagnosis and management of anaphylaxis. *Canadian Medical Association Journal*. 2003;169(4):307-12.
6. Estelle F, Simons R. Anaphylaxis, killer allergy: Long-term management in the community. *Journal of Allergy and Clinical Immunology*. 2006 Feb;117(2):367-77.

7. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *Journal of Allergy and Clinical Immunology*. 2010 Jul;126(1):98-104.
8. Kemp SF, Lockey RF, Simons FER. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy*. 2008 Aug;63(8):1061-70.
9. Lieberman P, Decker W, Camargo CA, Jr., Oconnor R, Oppenheimer J, Simons FE. SAFE: a multidisciplinary approach to anaphylaxis education in the emergency department. *Ann Allergy Asthma Immunol*. 2007 Jun;98(6):519-23.
10. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 Update. *JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY*. 2010;126(3):477-80+e1-e42.
11. Matasar MJ, Neugut AI. Epidemiology of anaphylaxis in the United States. *Current Allergy and Asthma Reports*. 2003 Jan;3(1):30-5.
12. McLean-Tooke APC, Bethune CA, Fay AC, Spickett GP. Adrenaline in the treatment of anaphylaxis: What is the evidence? *BRITISH MEDICAL JOURNAL*. 2003;327(7427):1332-5.
13. Moneret-Vautrin DA, Flabbee J, Morisset M, Beaudouin E, Kanny G. Epidemiology of prelethal and lethal anaphylaxis. *Revue Francaise D Allergologie Et D Immunologie Clinique*. 2004 Apr;44(3):315-22.
14. Moneret-Vautrin DA, Morisset M, Flabbee J, Beaudouin E, Kanny G. Epidemiology of life-threatening and lethal anaphylaxis: a review. *Allergy*. 2005 Apr;60(4):443-51.
15. Sheikh A, Shehata Yasser A, Brown Simon GA, Simons FER. Adrenaline (epinephrine) for the treatment of anaphylaxis with and without shock. *Cochrane Database of Systematic Reviews: Reviews 2008 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 101002/14651858CD006312pub2*.
16. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Golden DBK, Finkelman FD, et al. Risk assessment in anaphylaxis: Current and future approaches. *Journal of Allergy and Clinical Immunology*. 2007 Jul;120(1):S2-S24.
17. Simons FER, Frew AJ, Ansotegui IJ, Bochner BS, Golden DBK, Finkelman FD, et al. Practical allergy (PRACTALL) report: risk assessment in anaphylaxis. *Allergy*. 2008 Jan;63(1):35-7.
18. Soar J. Emergency treatment of anaphylaxis in adults: Concise guidance. *Clinical Medicine, Journal of the Royal College of Physicians of London*. 2009;9(2):181-5.
19. Soar J, Pumphrey R, Cant A, Clarke S, Corbett A, Dawson P, et al. Emergency treatment of anaphylactic reactions - Guidelines for healthcare providers. *Resuscitation*. 2008 May;77(2):157-69.
20. Wasserman S, Chad Z, Francoeur MJ, Small P, Stark D, Vander Leek TK, et al. Management of anaphylaxis in primary care: Canadian expert consensus recommendations. *ALLERGY*. 2010 Sep;65(9):1082-92.

List of studies with potential relevance for the cost-effectiveness analysis

1. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY*. 2004;113(3):536-42.
2. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008 Feb;63(2):226-32.
3. Brown AFT, McKinnon D. Emergency department anaphylaxis: A review of 142 patients in a single year. *Journal of Allergy and Clinical Immunology*. 2001 Nov;108(5):861-6.
4. Cardenas GA, Deitcher SR. Risk of anaphylaxis after reexposure to intravenous lepirudin in patients with current or past heparin-induced thrombocytopenia. *Mayo Clin Proc*. 2005 Apr;80(4):491-3.
5. Cianferoni A, Novembre E, Mugnaini L, Lombardi E, Bernardini R, Pucci N, et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). *Annals of Allergy Asthma & Immunology*. 2001 Jul;87(1):27-32.
6. Clark S, Bock SA, Gaeta TJ, Brenner BE, Cydulka RK, Camargo CA. Multicenter study of emergency department visits for food allergies. *Journal of Allergy and Clinical Immunology*. 2004 Feb;113(2):347-52.
7. Clark S, Long AA, Gaeta TJ, Camargo CA. Multicenter study of emergency department visits for insect sting allergies. *Journal of Allergy and Clinical Immunology*. 2005 Sep;116(3):643-9.
8. De Silva IL, Mehr SS, Tey D, Tang MLK. Paediatric anaphylaxis: A 5 year retrospective review. *Allergy: European Journal of Allergy and Clinical Immunology*. 2008;63(8):1071-6.
9. Dibs SD, Baker MD. Anaphylaxis in children: A 5-year experience. *Pediatrics*. 1997 Jan;99(1):E71-E5.
10. Dietrich W, Ebell A, Busley R, Boulesteix AL. Aprotinin and anaphylaxis: Analysis of 12,403 exposures to aprotinin in cardiac surgery. *Annals of Thoracic Surgery*. 2007 Oct;84(4):1144-50.
11. Dietrich W, Spath P, Ebell A, Richter JA. Prevalence of anaphylactic reactions to aprotinin: Analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *Journal of Thoracic and Cardiovascular Surgery*. 1997 Jan;113(1):194-201.
12. Dietrich W, Spath P, Zuhlsdorf M, Dalichau H, Kirchhoff PG, Kuppe H, et al. Anaphylactic reactions to aprotinin reexposure in cardiac surgery: Relation to antiaprotinin immunoglobulin G and E antibodies. *ANESTHESIOLOGY*. 2001;95(1):64-71.
13. Ellis AK, Day JH. Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients. *Ann Allergy Asthma Immunol*. 2007 Jan;98(1):64-9.

14. Erlewyn-Lajeunesse M, Dymond S, Slade I, Mansfield HL, Fish R, Jones O, et al. Diagnostic Utility of Two Case Definitions for Anaphylaxis A Comparison Using a Retrospective Case Notes Analysis in the UK. *Drug Safety*. 2010;33(1):57-64.
15. Estes O, Sala Cunill A, Guilarte M, Labrador M, Luengo O, Cardona V, editors. A review of anaphylaxis management in the emergency room. *Allergy: European Journal of Allergy and Clinical Immunology Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom Conference Start: 20100605 Conference End: 20100609 Conference: 29th Congress of the European Academy of Allergy and Clinical Immunology, EAACI London United Kingdom Conference Start: 20100605 Conference End: 20100609 Conference Publication: (varpagings) 65 (pp 589-590), 2010 Date of Publication: June 2010; 2010.*
16. Flabbee J, Petit N, Jay N, Guenard L, Codreanu F, Mazeyrat R, et al. The economic costs of severe anaphylaxis in France: An inquiry carried out by the Allergy Vigilance Network. *Allergy: European Journal of Allergy and Clinical Immunology*. 2008;63(3):360-5.
17. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol*. 2010 May;125(5):1098-104.e1.
18. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940 000 inhabitants of the Swiss Canton Bern. *Clinical and Experimental Allergy*. 2004 Feb;34(2):285-90.
19. Hompes S, Scherer K, Kohli A, Rueff F, Mahler V, Lange L, et al. Food anaphylaxis: Data from the anaphylaxis register. [German]. *Allergo Journal*. 2010;19(4):234-42.
20. Korenblat P, Lundie MJ, Dankner RE, Day JH. A retrospective study of epinephrine administration for anaphylaxis: how many doses are needed? *Allergy Asthma Proc*. 1999 Nov-Dec;20(6):383-6.
21. Lang DM, Alpern MB, Visintainer PF, Smith ST. GENDER RISK FOR ANAPHYLACTOID REACTION TO RADIOGRAPHIC CONTRAST-MEDIA. *Journal of Allergy and Clinical Immunology*. 1995 Apr;95(4):813-7.
22. Laporte JR, de Latorre FJ, Gadgil DA, Chandrasekhar DV, Laszlo A, Retsagi G, et al. An epidemiologic study of severe anaphylactic and anaphylactoid reactions among hospital patients: Methods and overall risks. *Epidemiology*. 1998 Mar;9(2):141-6.
23. Laporte JR, de Latorre J, Laszlo A, Retsagi G, Gadgil DA, Chandrasekhar DV, et al. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiology and Drug Safety*. 2003 Apr-May;12(3):195-202.
24. Laxenaire MC. Epidemiology of anesthetic anaphylactoid reactions. Fourth multicenter survey (July 1994-December 1996). [French]. *Annales francaises d'anesthesie et de reanimation*. 1999;18(7):796-809.
25. Manivannan V, Campbell RL, Bellolio MF, Stead LG, Li JTC, Decker WW. Factors associated with repeated use of epinephrine for the treatment of anaphylaxis. *Annals of Allergy, Asthma and Immunology*. 2009;103(5):395-400.

26. McIntyre CL, Sheetz AH, Carroll CR, Young MC. Administration of epinephrine for life-threatening allergic reactions in school settings. *PEDIATRICS*. 2005;116(5):1134-40.
27. Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children--a questionnaire-based survey in Germany. *Allergy*. 2005 Nov;60(11):1440-5.
28. Mulla ZD, Simon MR. Hospitalizations for anaphylaxis in Florida: Epidemiologic analysis of a population-based dataset. *International Archives of Allergy and Immunology*. 2007;144(2):128-36.
29. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States - An investigation into its epidemiology. *Archives of Internal Medicine*. 2001 Jan;161(1):15-21.
30. Noimark L, Khakoo GA, Summerfield A, Gardner J, Cox H, Warner JO, editors. Awareness of adrenaline auto-injector availability and emergency management in school among parents of children with allergy. *Clinical and Experimental Allergy Conference: British Society for Allergy and Clinical Immunology Annual Conference 2009 Nottingham United Kingdom Conference Start: 20090629 Conference End: 20090701 Conference: British Society for Allergy and Clinical Immunology Annual Conference 2009 Nottingham United Kingdom Conference Start: 20090629 Conference End: 20090701 Conference Publication: (varpagings) 39 (12) (pp 1949-1950), 2009 Date of Publication: December 2009; 2009.*
31. Ross MP, Ferguson M, Street D, Klontz K, Schroeder T, Luccioli S. Analysis of food-allergic and anaphylactic events in the national electronic injury surveillance system. *Journal of Allergy and Clinical Immunology*. 2008 Jan;121(1):166-71.
32. Rudders SA, Banerji A, Corel B, Clark S, Camargo CA, Jr. Multicenter study of repeat epinephrine treatments for food-related anaphylaxis. *PEDIATRICS*. 2010 Apr;125(4):e711-8.
33. Rueda GM, Guilarte M, Luengo O, Sala A, Labrador M, Cardona V. Impact of adrenaline auto-injector prescription in anaphylaxis. *Allergy*. 2008;63:734.
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List of excluded studies with reasons for exclusion

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No relevant data (no relevant studies identified).

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No relevant data.

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No relevant data.

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Not anaphylaxis.

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No relevant data.

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No relevant data.

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Wrong study type

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Foreign language paper.

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No relevant data.

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Wrong study type.

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No relevant data.

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No relevant data.

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Stock in British Library goes up to 2009, 26(3)

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Closed building at the British Library, not available until February 2012.

4.Hoigne R, Schlumberger HP, Vervloet D, Zoppi M. EPIDEMIOLOGY OF ALLERGIC DRUG-REACTIONS. Monographs in Allergy. 1993;31:147-70.

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8.Simons KJ, Simons FER. Epinephrine and its use in anaphylaxis: current issues. Curr Opin Allergy Clin Immunol. 2010 Aug;10(4):354-61.

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Closed building at the British Library, not available until February 2012.

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Ordered from British Library in London. A day later notification that this is missing stock.

Appendix 4: Search strategy for economic evaluations

The following sources were searched to identify economic evaluations and quality of life data.

These searches were conducted in February/March 2011.

OvidSP MEDLINE <1948-2011/03/wk 2> , searched 17/03/2011.

- 1 economics/ (25965)
- 2 exp "costs and cost analysis"/ (154360)
- 3 economics, dental/ (1814)
- 4 exp "economics, hospital"/ (17009)
- 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 pharmaco-economic\$.ti,ab. (327719)
- 9 (expenditure\$ not energy).ti,ab. (13900)
- 10 (value adj1 money).ti,ab. (18)
- 11 budget\$.ti,ab. (14162)
- 12 or/1-11 (439089)
- 13 ((energy or oxygen) adj cost).ti,ab. (2243)
- 14 (metabolic adj cost).ti,ab. (578)
- 15 ((energy or oxygen) adj expenditure).ti,ab. (12794)
- 16 or/13-15 (15012)
- 17 12 not 16 (435668)
- 18 letter.pt. (707514)
- 19 editorial.pt. (270646)
- 20 historical article.pt. (271900)
- 21 or/18-20 (1237508)
- 22 17 not 21 (411802)
- 23 animals/ not (animals/ and humans/) (3467241)
- 24 22 not 23 (388655)
- 25 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (85022)
- 26 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15572)

27 (Anaphyla\$ or pseudoanaphyla\$).ti,ab,ot,hw. (24719)

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 (108202)

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 13.1.11]. Available from: http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

OvidSP Medline In-Process Citations <up to 2011/03/16> and OvidSP Medline Daily Update < up to 2011/03/16>, searched 17/03/2011]

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 pharmaco-economic\$).ti,ab. (21859)

9 (expenditure\$ not energy).ti,ab. (657)

10 (value adj1 money).ti,ab. (2)

11 budget\$.ti,ab. (1252)

12 or/1-11 (23138)

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 (22934)

18 letter.pt. (15937)

- 19 editorial.pt. (9720)
- 20 historical article.pt. (115)
- 21 or/18-20 (25758)
- 22 17 not 21 (22640)
- 23 animals/ not (animals/ and humans/) (1312)
- 24 22 not 23 (22627)
- 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 13.1.11]. Available from:
http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

OvidSP Embase <1980-2011/wk 10>, searched 17/03/2011.

- 1 health-economics/ (29979)
- 2 exp economic-evaluation/ (164685)
- 3 exp health-care-cost/ (158213)
- 4 exp pharmacoeconomics/ (135242)
- 5 or/1-4 (379306)
- 6 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (422362)
- 7 (expenditure\$ not energy).ti,ab. (16881)

8 (value adj2 money).ti,ab. (884)

9 budget\$.ti,ab. (17911)

10 or/6-9 (440596)

11 5 or 10 (666254)

12 letter.pt. (721412)

13 editorial.pt. (367270)

14 note.pt. (436494)

15 or/12-14 (1525176)

16 11 not 15 (596935)

17 (metabolic adj cost).ti,ab. (638)

18 ((energy or oxygen) adj cost).ti,ab. (2507)

19 ((energy or oxygen) adj expenditure).ti,ab. (14885)

20 or/17-19 (17369)

21 16 not 20 (593002)

22 animal/ or animal experiment/ (3059048)

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. (4688188)

24 or/22-23 (4688188)

25 exp human/ or human experiment/ (12277839)

26 24 not (24 and 25) (3764868)

27 21 not 26 (567207)

28 Hypersensitivity/ or exp Drug hypersensitivity/ or exp drug eruptions/ or Hypersensitivity-Reaction/ or Immediate-Type-Hypersensitivity/ (88290)

29 Eosinophilic esophagitis/ or Food-Allergy/ or Allergic-Pneumonitis/ or Allergic-Bronchopulmonary-Aspergillosis/ (18423)

30 Anaphylactic-Shock/ or Anaphylactoid-Purpura/ or Passive-Skin-Anaphylaxis/ or Skin-Anaphylaxis/ or Anaphylaxis/ (32909)

31 (Anaphyla\$ or pseudoanaphyla\$.ti,ab,ot,hw. (39414)

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 (137588)

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 17.3.11].

Available from: <http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#embase>]

Health Technology Assessment (HTA) (Internet) <2000-2011/03/16> via

<http://www.crd.york.ac.uk/crdweb/>. Searched 17/03/2011.

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 (econom* OR cost OR costs OR costly OR costing OR price OR prices OR pricing OR pharmaco-economic* OR budget*) 35538

32 (expenditure* NOT energy) 738

33 (value NEAR money) 204

34 #31 or #32 or #33 35555

35 #30 and #34 396

[HTA search retrieved 28 records.]

NHS Economic Evaluation Database (NHS EED) (Internet) <2000-2011/03/16> via <http://www.crd.york.ac.uk/crdweb/>. Searched 17/03/2011.

- 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

[NHS EED search retrieved 299 records.]

Science Citation Index (SCI) (Web of Science) <1970-2011/02/12>, searched 14/02/2011.

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 pharmaco-economic*)

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*)

[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 13.1.11]. Available from:

http://www.crd.york.ac.uk/crdweb/html/helpdoc.htm#MEDLINE_NHSEED]

EBSCO Cinahl <1981-2011/02/18>, searched 23/02/2011

S13 s9 and s12 Limiters - Exclude MEDLINE records (651)

S12 s10 not s11 (158410)

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*)) (159067)

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+") (20402)

Appendix 5: Economic evaluation quality assessment

Study design	Krasnick 1996	Shaker 2007	Desai 2009
(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 are 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
	2	3	3
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 are 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
	5	5	0
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 confidence intervals 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
	4	10	2
	n=11	n=18	n=5

Appendix 6: Table of model parameters

Number	Parameter	Name parameter in model	Distribution type	Min	Most likely	Max	Sources
	Population characteristics (paragraph 2.4.1)						
1	cohort start age	startage	N/A		30		Assumption
2	proportion of cohort male	pmale	N/A		0.5		Health Hospital Episode Statistics (see section on General model assumptions, paragraph 2.3)
	Rate of recurrence (paragraph 2.4.1)						
3	annual rate of recurrence of anaphylaxis due to drugs with <u>SS</u> **	dprecurdrugSS	Triangular	0	0.001	0.002	EO*
4	annual rate of recurrence of anaphylaxis due to food with <u>SS</u>	dprecurfoodSS	Triangular	0	0.01	0.02	EO and based on Ewan et al. 2001 (Page 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 (Page 112 table 1: Severe follow-up reaction grade 5 r=3 (0.5%), n=567 (100%))
5	annual rate of recurrence of anaphylaxis due to food with <u>SC</u> ***	drecurfood	Triangular	0.05	0.11	0.16	EO and based on Mullins 2003 (Figure 1, page 1037)
6	annual rate of recurrence of idiopathic anaphylaxis with <u>SC</u>	drecuridio	Triangular	0.05	0.28	0.51	EO and based on Mullins 2003 (Figure 1, page 1037)
7	annual rate of recurrence of anaphylaxis due to drugs with <u>SC</u>	drecurdrug	Triangular	0.05	0.12	0.19	EO and based on Mullins 2003 (Figure 1, page 1037)
8	annual rate of recurrence of anaphylaxis due to insect sting with <u>SC</u>	drecurinsect	Triangular	0.05	0.10	0.15	EO and based on Gonzalez-Perez 2010 (page 1101-1102 Last paragraph page 1101: "Anaphylaxis is associated with high risk of recurrence but is highly unpredictable. Estimated rate:

							0.06 to 0.11 episodes per year")
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*EO= expert opinion, **SS= specialist service, ***SC=standard care

Number	Parameter	Name parameter in model	Distribution type	r in categories	n	r	Sources
	Trigger probability (paragraph 2.4.3)						
9	probability incidence due to idiopathic	didio	Beta		343	103	Gonzalez-Perez 2010 (Table V page 1104) = 30%
10	probability incidence due to insect given not idiopathic	dinsect	Beta		240	46	Gonzalez-Perez 2010 (Table V page 1104) = 13.4%
11	probability incidence due to drug given not idiopathic and not insect in child	ddrugchild	Beta		87	19	Capps et al 2010 (Table 1 page 655) = 12.4%
12	probability incidence due to drug given not idiopathic and not insect in adult	ddrugadult	Beta		303	236	Capps et al 2010 (Table 1 page 655) = 44.1%
	Mortality (paragraph 2.4.4)						
13	Annual probability of dying given anaphylaxis and presence of emergency services and current adrenaline injector use	ddieanaph	Beta		3517	20	Soar et al 2008, HES 2010
				r in categories (2.1-4.5, 4.6-9.9, 10-20 and >20 mins)			
14	Time to die, food	dtimediefood	Dirichlet	(0;0;9;50)			Soar et al 2008
15	Time to die, drug	dtimediedrug	Dirichlet	(0;2;4;7)			Soar et al 2008
16	Time to die, insect	dtimedieinsect	Dirichlet	(2;420;19)			Soar et al 2008
				r in categories (<8, 8-18 and >18 mins)			
17	Ambulance response time, Category A	dtimeA	Dirichlet	(1,442,519;437,973;60,160)		n/a**	NHS Information Centre 2010
18	Ambulance response	dtime19B	Beta		2,559,126	2,322,793	NHS Information

	time, Category B						Centre 2010
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*EO= expert opinion, **n/a= not applicable

Number	Parameter	Name parameter in model	Distribution type	n	r	Min	Most likely	Max	Sources
19	Probability of correct use of injector with <u>SC</u> *	dpinjector	Beta	116	53				Capps et al 2010 (n= table 3 page 655 at any time r=before ambulance arrived)
20	Probability use injector correctly with <u>SC</u> in child	dinjectorchild	Beta	15	10				Capps et al 2010 (n= table 3 page 655, at any time r=before ambulance arrived (child))
21	Probability use injector correctly with <u>SC</u> in adult	dinjectoradult	Beta	101	43				Capps et al 2010 (n= table 3 page 655, r=before ambulance arrived (adult))
22	probability use injector correctly with <u>SS</u> **	dpinjectorSS	Triangular				1		Assumption
	Idiopathic treatment (paragraph 2.4.5)								
23	Median time to remission in frequent idiopathic	dmedianfreq	Triangular			2	4	6	Based on data from Krasnick et al 1996
24	Median time to remission in infrequent idiopathic	dmedianinfreq	Triangular			1	1.5	2	Based on data from Krasnick et al 1996
25	Proportion of idiopathic that are frequent	dfreqidio	Beta	56	28				Krasnick et al 1996
	Venom immunotherapy (paragraph 2.4.6)								
26	Effectiveness of VIT***	dpeffectVIT	Triangular			0.75	0.85	0.95	Based on Krishna et al 2010
27	Dropout of VIT	dropout	Triangular			0.1	0.2	0.3	Based on Goldberg et al 2000
28	Uptake of VIT	duptakeVIT	Triangular			0.4	0.6	0.8	Based on Cox et al 2011
	Utility (paragraph 2.4.7)								
29	Utility decrement due to at risk	duatrisk	Triangular			0.06	0.08	0.1	Based on Voordouw et al 2010
30	Duration of recurrence	ddurationrecur	Uniform			1	n/a**	9	Based on Neuner et al 2003

31	Utility factor with SS	duSSimprove	Triangular			0	0.25	0.5	Assumption based on EO
32	Utility factor with adrenaline injector	duAlimprove	Triangular			0	0.25	0.5	Assumption based on EO

*SC=standard care, *SS= specialist service, ***VIT= venom immunotherapy, ****n/a= not applicable

Number	Parameter	Name parameter in model	Distribution type	Mean	SE#	Min	Most likely	Max	Sources
	Costs (paragraph 2.4.8)								
33	mean cost of inpatient care	dcostrecur	Normal	£469.88	£37.585				HES**
34	mean cost of adrenaline injector	cinjector	n/a	£28.97	n/a				BNF 61*****
35	costs of two SS*** sessions (each about £200)	cSS	n/a	£400	n/a				EO**** (Commissioner in UK)
36	duration of VIT***** (years)	ddurationVIT	Triangular			2	3	4	Based on Diwaker et al 2008
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 EO
38	for VIT maintenance treatment average cost for bee and wasp extract	cVITmaintenance	n/a	£60	n/a				BNF 61
39	for VIT induction treatment	cVITinitial	n/a	£70	n/a				BNF 61
40	number of weeks between VIT maintenance doses	nVITmaintenance	Triangular			4	6	8	EO and Cox et al 2011
41	cost of prednisolone per mg	cpred	n/a	£0.02	n/a				BNF 61
42	duration of prednisolone course in months	ddurationpred	Uniform			2	n/a	3	Simons et al 2010
43	start dose of prednisolone in mg	dstartdosepred	Uniform			60	n/a	100	Simons et al 2010, Lieberman et al 2010
44	duration of start dose of	dstartduration	Uniform			1	n/a	2	Simons et al 2010, Lieberman

	prednisolone								et al 2010
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*n/a= not applicable, **HES= Health Hospital Episode Statistics, ***SS= specialist service, ****EO = expert opinion, *****VIT= venom immunotherapy, ##BNF61= British National Formulary, #SE=standard error