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Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode – Protocol for systematic review and economic modelling

1. Title of project

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

2. Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd. Assessment Group.

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Plain English Summary

The Department of Health has asked NICE: 'to produce a short clinical guideline on the initial assessment and the decision to refer following emergency treatment for anaphylactic episode'. The population concerns adults, young people and children who receive emergency treatment for suspected anaphylaxis.

The systematic review and economic modelling work of the EAG will address the following questions:

Within this population, which people are at high risk of anaphylactic episodes? For which people would further anaphylactic episodes have significant impact? Which people can be identified as needing special consideration?

What are the effects of history taking, including signs and symptoms, and physical examination in identifying the possible cause?

What are the effects of providing adrenaline auto-injectors, including by whom.

After assessment, when should referral take place?

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 auto-injectors?

3. Decision problem

3.1. Objectives

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.

4. Methods

4.1. General Inclusion and exclusion criteria for all questions

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

4.2. Search strategy

The following databases will be searched for relevant studies from inception to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- CINAHL
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (CRD website)
- Health Technology Assessment Database (HTA) (CRD website)
- NHS Economic Evaluations Database
- Science Citation Index (SCI) (Web of Science)

Identified references will be downloaded in Endnote X4 software for further assessment and handling.

References in retrieved articles and relevant systematic reviews will be checked.

Search strategies will be developed specifically for each database and the keywords associated with anaphylaxis shall be adapted according to the configuration of each database.

No restrictions on language or publication status will be applied. Limits will be applied to remove animal studies. Searches will take into account generic and other product names for the intervention. Examples of the MEDLINE search strategies to be used are presented in Appendix 1.

4.3. Data extraction strategy

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess

these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.
Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using the NICE Guidelines Manual evidence tables. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4. Quality assessment strategy

Quality assessment will be done using the appropriate NICE Guidelines Manual methodology checklists.
The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. In addition, if enough data are available from the included studies, quality components will be included as covariates in any multivariable analyses, to investigate their possible association with test performance. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

4.5. Methods of analysis/synthesis

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed.

A general overall summary of the evidence base will be presented identifying of the types of studies, their characteristics and methodological quality. Studies will then be grouped according to risk factor and for each identified risk factor, a summary of the number, type and quality of the studies assessing that risk factor will be reported, along with the number of studies reporting a statistically significant effect using a multivariate analysis. Details of the multivariate model (Cox regression model; interval censored survival model; Cox discrete survival model; logistic regression model) and its findings will also be summarised in each case. Studies will be assessed and described according to whether they have included relevant and important clinical, procedural and factors in their model.

It is likely that there will be systematic differences (heterogeneity) between the included studies. However, if studies are considered to be statistically similar and clinically similar (based on the study design, patient population), then statistical pooling of effect measures will be considered.

For prognosis / risk factors this will involve pooling adjusted odds ratios (OR) for dichotomous data or hazard ratios (HR) for time to event data, for each identified risk factor, using a random effects model. Effect sizes will be reported with 95% confidence intervals (CIs).

For the effects of interventions we will use standard Cochrane Collaboration methods of meta-analysis using Review Manager, where appropriate and possible.
Statistical heterogeneity will be assessed by measuring the degree of inconsistency between the study results (I^2). This measure (I^2) describes the percentage of total variation across studies that is due to heterogeneity rather than the play of chance. The value of I^2 lies between 0% and 100%, and an often used, simplified categorisation of heterogeneity is low, moderate, and high, corresponding to I^2 values of 25%, 50%, and 75%. For this review, studies will be considered sufficiently similar for the purposes of pooling if I^2<75%.

A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5 CEA

5.1 Technologies and population

Estimates of costs and effectiveness are those that are relevant for decision making, in this case the recommendations within the guideline regarding choice of:

1. referral to specialist service (SS) versus no referral (SC)
2. diagnostic workup (Test x) from possible set X to test for anaphylaxis or not
3. diagnostic workup (Test y) from possible set Y to test for cause of anaphylaxis
4. supply of adrenaline auto-injectors (AI) or not (NA)

Because the consequences of choice sets (1), (2) and (3) are dependent on whether someone receives AI or NA, they will be synthesised as part of an overall decision analytic model (DAM) that estimates cost and effectiveness over a lifetime for the population of those with suspected anaphylaxis who survive the index episode.

5.2 CEA Review

This will include a systematic review of the four comparisons, although the scope might be widened to include any DAM study in the anaphylaxis population in order to learn from the latest methods. Studies will obtained firstly by using the search strategies described above and then through citation and hand searching.

5.3 DAM structure

A CEA employs a specific type of DAM, whereby evidence is synthesized according to a mathematical relationship between various parameters[1] in order to calculate final outcomes i.e. outcomes of interest in decision making. In a CEA, final outcomes are measures of cost and effect, which in the case of NICE is Quality Adjusted Life Years (QALYs) [2]. Put simply, construction of the DAM is in two parts, the model structure itself, which is the relationship between parameters and collection of evidence to inform those parameters i.e. parameterization[3] (see section 5.4). There are two basic means of expressing the structure in order to express the natural history and care pathway and thus the effect of any technologies, either as events (and time to event) or health states (and time in health state)[4]. However, they are two sides of the same coin in that an event is what changes a health state e.g. having an episode of suspected anaphylaxis (SA) changes the health state of pre SA to post SA, thus implying the potential for changes in cost and quality of life (QoL). States can also determine the probability of events so that the probability of SA could depend on whether it is the first or second event etc. State transition model is the term used to describe such a model where change in state is called transition and probabilities of events (change in state) in some time period are called transition probabilities[5]. The time period is referred to as cycle length such that the total time horizon e.g. in years would be the number of years divided by cycle length. Such models are often called Markov models, although strictly this relies on the assumption (Markov assumption) that transition probabilities are independent of state. Markov models can be used to estimate the rate of events and expected time in state, such as life expectancy as well as cost. Also, by weighting time in state by a value between 0 and 1, the expected value, which is the sum of the product of probability of state multiplied by value, can be calculated. If each of these values is a utility, i.e. indicating preference for state, the expected utility can be calculated, assuming independence between utility as a function of time and state[2]. This expected utility is usually referred to as expected number of QALYs where utility is the quality term and is the preferred outcome for decision making by NICE[6].

As for any CEA DAM the starting point is a care pathway, which shows the possible relationships between health states (event sequences). To address the three technology comparisons set out above it has already been stated that a single model is required, but for each comparison a different sub-population within the initial health state (in the first cycle). For the first comparison SS vs SC, the population is individuals who have presented as an

emergency admission (EA) with suspected anaphylaxis and survive (SA). Some of these will have anaphylaxis, which implies a probability of anaphylaxis given SA i.e. the prevalence of anaphylaxis in the population of SA. One might consider that standard care (SC) is to discharge i.e. not refer to specialist services (SS) for diagnosis, advice and adrenaline. Costs of each type of service provision will therefore be required.

Given referral, one major component of SS is diagnosis, which implies a comparison of the probability of detecting anaphylaxis given diagnostic workup (test) X where test X is a set of tests each of which vary by the set of predictor variables e.g. age, sex, family history, presence of asthma etc.

For the anaphylaxis subpopulation (SAA) there will be a rate of recurrence of anaphylaxis EA given SS (e.g. due to better advice) and a rate of recurrence given SC. They are likely to differ due to differential advice i.e. secondary prevention. If we then assume that the false positive rate i.e. the probability of diagnosis of anaphylaxis given no anaphylaxis (SAN) is negligible and the prevalence of anaphylaxis in the SA population also high then no further information is required on the SAN population. Otherwise the rate of recurrence of EA for SAN will be required or at least of SA together with the prevalence of anaphylaxis in the SA population.

The second major diagnostic component, following SAA diagnosis is that to determine cause, which again will affect treatment/advice and thus rate of recurrence.

Finally, those who suffer anaphylaxis recurrence might then have outcomes such as admission to ES as well as the possibility of death, thus implying a probability of outcome X given anaphylaxis, but this will depend on whether they receive adrenaline or the timing of receipt, which depends on the choice between AI or NA.

This care pathway can be summarised by the following:

For non-anaphylaxis sub-group, SAN, there will be a rate of recurrence, but only if there is a significant false positive rate

For the anaphylaxis sub-group, SAA, there will be a rate of recurrence, which is modified by:

1. any change from SC to SS (due to better general advice/treatment)
2. any change in diagnostic work-up to diagnose condition, Test x
3. any change in diagnostic work-up to diagnose cause, Test y
4. AI vs NA

5.4 Parameterisation

The care pathway summary shows that parameter estimates will be sought for the following relative risks of recurrence:

1. SC vs SS
2. Test a vs b where a, b are in the set X

3. Test c vs d where c, d are in the set Y
4. AI vs NA

These will be obtained from the systematic reviews specified above. A baseline risk of recurrence ie for SAA given SC, current testing and NA, will be estimated from baseline data estimated from one of the systematic reviews. Methods of quality assessment will applied to select study data, paying particular attention to size and external validity (degree of similarity to the index population and care pathway). Where there are several sources, advice from clinical experts will also be taken on the selection of study used to obtain this data and sensitivity analysis used (see Analysis below).

Data will be required on the cost of SS and how these might vary depending on the testing regime and location/staffing. It will also be required on the cost of ES and the prevalence of use of each of the various types e.g. ambulance, GP or self presentation to A+E. The searches described above to obtain CEA studies will be used to find literature based sources either used in extant CEAs or in cost only studies. Further hand and citation searching will also be done as required.

In order to estimate QALYs utility data will be sought. The NICE Reference Case[6] is that they be estimated using the EQ-5D instrument[7]. In the base case it will be assumed that anaphylaxis treatment does not affect quality of life except very briefly and therefore, general population estimates of EQ-5D, adjusted for any difference in age or sex distribution, will be used[7].

5.5 Analysis

The DAM will be constructed and populated (with parameter values) in TreeAge Pro 2010. Cohort analysis (essentially adding up values for each health state weighted by their probabilities) will allow estimation of the expectation over time of cost, QALYs and life expectancy. Expected number of events e.g. MIs can also be estimated.

Where there is any variability in parameters e.g. of time horizon, lifetime forming the base case or discount rate, one way sensitivity analysis will be performed. This type of analysis will also be used where there are multiple data sources for one parameter, which cannot be combined using meta-analysis.

Probabilistic sensitivity analysis (PSA) will be performed to account for uncertainty, essentially due to sampling error[8]. This uses Monte Carlo Simulation (MCS) in order to sample simultaneously from the sampling distribution of each parameter, thus enabling the expected value of cost and effectiveness given the joint uncertainty. Therefore, where

possible, parameter values will obtained as not only a point estimate e.g. relative risk, but also a standard error or information to estimate a standard error (e.g. the number at risk of event and number of events and not only the probability). Expert opinion will be sought where data is unavailable.

Sensitivity analysis will also be conducted regarding the cost effectiveness threshold in terms of the probability of being cost effective (based on the results of the MCS), which can be shown as a Cost effectiveness acceptability curve (CEAC)[8].

5.6 Presentation of results

Results will be presented as follows:

- Expected cost for each of four comparisons.
- Expected QALYs/LYGs (Life Years Gained) for each of four comparisons
- Incremental cost and incremental QALYs/LYGs
- CEAC for each of four comparisons

5.7 References

1. Weinstein, M.C., et al., Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices-Modeling Studies. Value Health, 2003. 6: p. 9 - 17.
2. Drummond, M.F., et al., Methods for the Economic Evaluation of Health care programmes. Oxford medical Publications. 1997, Oxford: Oxford University press.
3. Griffin, S., K. Claxton, and M. Sculpher, Decision analysis for resource allocation in health care. Journal of Health Services Research & Policy, 2008. 13: p. 23-30.
4. Karnon, J., A. Brennan, and R. Akehurst, A Critique and Impact Analysis of Decision Modeling Assumptions. Med Decis Making, 2007. 27(4): p. 491-499.
5. Briggs, A. and M. Sculpher, An introduction to Markov modelling for economic evaluation. Pharmacoeconomics, 1998. 13(4): p. 397-409.
6. National Institute for Health and Clinical Excellence, Guide to the methods of technology appraisal. 2008, National Institute for Health and Clinical Excellence: London.
7. Dolan, P. and J. Roberts, To what extent can we explain time trade-off values from other information about respondents? Social Science & Medicine, 2002. 54(6): p. 919-929.
8. Briggs, A., Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. Value Health, 2005. 8: p. 1 - 2.

6. Competing interests of authors

None

Appendix 1: Search strategies

Clinical assessment, history taking, identification of possible cause

Medline (OvidSP): 1948-2011/1/wk 1
Searched 18.1.11

1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83082)
2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15242)
3 (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24105)
4 ((severe$ 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$)).ti,ab,ot,hw. (4297)
5 ((severe$ 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$)).ti,ot,ab. (2240)
6 or/1-5 (105746)
7 exp Emergency Treatment/ (79909)
8 (Accident adj2 emergency).ti,ab,ot,hw. (3465)
9 exp Emergency Medical Services/ (75190)
10 (Emergenc$ adj3 (treat$ or admit$ or admission$ or episode$ or case$ or patient$ or department$ or room$ or rooms or care or medic$ or intervene$ or therap$ or hospital$ or service$)).ti,ab,ot,hw. (113943)
11 (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or intervene$ or therap$ or patient$)).ti,ab,ot,hw. (819)
12 (Accident adj2 emergency).ti,ab,ot,hw. (3465)
13 Triage$.ti,ab,ot,hw. (9744)
14 First aid$.ti,ab,ot,hw. (8183)
15 (First response$ or first respond$).ti,ab,ot,hw. (1524)
16 (Medical adj2 urgen$).ti,ab,ot,hw. (421)
17 Emergencies/ (30916)
18 (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (373)
19 (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (525)
20 or/7-19 (212368)
21 Physical Examination/ (24965)
22 ((clinical$ or physical$) adj2 (assess$ or exam$ or test$ or history or histories)).ti,ab,ot,hw. (166184)
23 exp medical history taking/ or cornell medical index/ (16075)
24 ((Medical$ or patient$) adj2 (histories or history)).ti,ab,ot,hw. (37926)
25 Anamnesis.ti,ab,ot,hw. (3336)
26 ((identif$ 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. (65066)

27 exp skin tests/ (50396)
28 (allerg$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (1977)
29 (Sensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (79713)
30 (hypersensitivit$ adj1 (test$ or investigat$)).ti,ab,ot,hw. (333)
31 ((skin or intradermal$ or intra-dermal$ or intracutaneous$ or epidermal$ or cutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (39934)
32 ((passive transfer or prausnitz kustner or kveim) adj2 (test$ or investigat$)).ti,ab,ot,hw. (434)
33 (RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (1170)
34 (prick adj1 (test$ or investigat$)).ti,ab,ot,hw. (6207)
35 ((patch or percutaneous$ or epicutaneous$) adj1 (test$ or investigat$)).ti,ab,ot,hw. (10425)
36 (CAP RAST adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (22)
37 (specific IgE adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (414)
38 Fluorenzymeimmunoassay$.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$)).ti,ab,ot,hw. (4425)
41 (radioimmunoassay$ adj2 (test or investigat$)).ti,ab,ot,hw. (316)
42 ((ImmunoCAP or Immuno-CAP) adj2 (test or assay$ or investigat$)).ti,ab,ot,hw. (38)
43 Skin end point titration.ti,ab,ot,hw. (13)
44 rinkel serial dilution titration.ti,ab,ot,hw. (1)
45 Challenge test$.ti,ab,ot,hw. (4121)
46 (mast cell tryptase adj2 (test$ or assay$ or investigat$)).ti,ab,ot,hw. (5)
47 or/21-46 (401066)
48 6 and 20 and 47 (268)
49 animals/ not (animals/ and humans/) (3394630)
50 48 not 49 (265)

<u>Auto-injectors</u>

Medline (OvidSP): 1948-2011/1/wk 1
Searched 18.1.11

1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83082)
2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15242)
3 (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24105)
4 ((severe$ 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$)).ti,ab,ot,hw. (4297)
5 ((severe$ 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$)).ti,ot,ab. (2240)
6 or/1-5 (105746)
7 ((IM or Intramuscul$ or Intra-muscul$) adj1 (Epinephrine or adrenaline)).ti,ab,ot,hw. (60)
8 (auto-inject$ or autoinject$).ti,ab,ot,hw. (378)

9 (epipen$ or epi-pen$ or anapen$ or ana-pen$ or twinject$ or twin-ject$ or jext$).ti,ab,ot,hw. (92)
10 ((self-medicat$ or selfmedicat$ or selfadminister$ or self-administer$ or selfinject$ or self-inject$) adj3 (Epinephrine or adrenaline)).ti,ab,ot,hw. (94)
11 or/7-10 (577)
12 6 and 11 (251)
13 animals/ not (animals/ and humans/) (3394630)
14 12 not 13 (247)

Referral
Medline (OvidSP): 1948-2011/1/wk 1
Searched 18.1.11

1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83082)
2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15242)
3 (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24105)
4 ((severe$ 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$)).ti,ab,ot,hw. (4297)
5 ((severe$ 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$)).ti,ot,ab. (2240)
6 or/1-5 (105746)
7 "referral and consultation"/ or gatekeeping/ (43965)
8 (Refer$ or consultation$ or Gatekeep$ or gatekeep$).ti,ab,ot,hw. (566736)
9 (Second opinion$ or 2nd opinion$).ti,ab,ot,hw. (1023)
10 (followup$ or follow-up$ or outpatient$ or out-patient$).ti,ab,ot,hw. (779292)
11 Outpatient Clinics, Hospital/ (12893)
12 (Allergist$ or aftercare or after-care).ti,ab,ot,hw. (8550)
13 aftercare/ (5911)
14 (Allerg$ clinic$ or Specialist clinic$).ti,ab,ot,hw. (1126)
15 or/7-14 (1300213)
16 6 and 15 (6418)
17 animals/ not (animals/ and humans/) (3394630)
18 16 not 17 (6199)
19 exp Emergency Treatment/ (79909)
20 (Accident adj2 emergency).ti,ab,ot,hw. (3465)
21 exp Emergency Medical Services/ (75190)
22 (Emergenc$ 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$)).ti,ab,ot,hw. (113943)
23 (Casualty adj2 (department$ or admit$ or admission$ or patient$ or case$ or care or medicat$ or intervene$ or therap$ or patient$)).ti,ab,ot,hw. (819)
24 (Accident adj2 emergency).ti,ab,ot,hw. (3465)
25 Triage$.ti,ab,ot,hw. (9744)
26 First aid$.ti,ab,ot,hw. (8183)

27 (First response$ or first respond$).ti,ab,ot,hw. (1524)
28 (Medical adj2 urgen$).ti,ab,ot,hw. (421)
29 Emergencies/ (30916)
30 (postepisod$ or postadmission$ or postadmit$ or postreaction$ or postevent$ or postincident$).ti,ab,ot,hw. (373)
31 (post adj (episod$ or admission$ or admit$ or reaction$ or event$ or incident$)).ti,ab,ot,hw. (525)
32 or/19-31 (212368)
33 18 and 32 (230)

Risk of recurrence
Medline (OvidSP): 1948-2011/1/wk 1
Searched 19.1.11

1 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83082)
2 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15242)
3 (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24105)
4 ((severe$ 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$)).ti,ab,ot,hw. (4297)
5 ((severe$ 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$)).ti,ot,ab. (2240)
6 or/1-5 (105746)
7 Recurrence/ (135125)
8 (Recrudescen$ or recur$ or repeat$ or re-occur$ or reoccur$ or subsequent$ or repetition$ or repeat$).ti,ab,ot,hw. (1085485)
9 (Future adj3 (episode$ or event$ or inciden$ or occur$ or experience$ or attack$ or bout$)).ti,ab,ot,hw. (4394)
10 or/7-9 (1089173)
11 risk/ or risk assessment/ or risk factors/ (594169)
12 (risk or risks or likelihood$).ti,ab,ot,hw. (1192600)
13 or/11-12 (1192600)
14 10 and 13 (142559)
15 6 and 14 (1158)
16 animals/ not (animals/ and humans/) (3394630)
17 15 not 16 (1120)

Cost-effectiveness search

Medline (OvidSP): 1948-2011/1/wk 1
Searched 19.1.11

1 economics/ (25783)
2 exp "costs and cost analysis"/ (151450)
3 economics, dental/ (1784)
4 exp "economics, hospital"/ (16683)

5 economics, medical/ (8226)
6 economics, nursing/ (3785)
7 economics, pharmaceutical/ (2150)
8 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (319490)
9 (expenditure$ not energy).ti,ab. (13593)
10 (value adj1 money).ti,ab. (16)
11 budget$.ti,ab. (13878)
12 or/1-11 (429081)
13 ((energy or oxygen) adj cost).ti,ab. (2195)
14 (metabolic adj cost).ti,ab. (566)
15 ((energy or oxygen) adj expenditure).ti,ab. (12457)
16 or/13-15 (14631)
17 12 not 16 (425734)
18 letter.pt. (690212)
19 editorial.pt. (263948)
20 historical article.pt. (266083)
21 or/18-20 (1208103)
22 17 not 21 (402320)
23 animals/ not (animals/ and humans/) (3394630)
24 22 not 23 (379955)
25 hypersensitivity/ or drug hypersensitivity/ or exp drug eruptions/ or hypersensitivity, immediate/ or anaphylaxis/ or asthma, aspirin-induced/ or eosinophilic esophagitis/ (83082)
26 food hypersensitivity/ or alveolitis, extrinsic allergic/ or aspergillosis, allergic bronchopulmonary/ or latex hypersensitivity/ (15242)
27 (Anaphyla$ or pseudoanaphyla$).ti,ab,ot,hw. (24105)
28 ((severe$ 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$)).ti,ab,ot,hw. (4297)
29 ((severe$ 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. (2240)
30 or/25-29 (105746)
31 24 and 30 (1024)

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

Economic Evaluations
NHS EED (internet): up to 2011/1/19
Searched 19.1.11

1 anaphyla* 79

NHS EED search retrieved 38 references.