Appendix F Full health economic report

Title

A cost-effectiveness analysis (CEA) comparing no referral versus referral to specialist allergy clinic as well as the prescription of adrenaline injectors for suspected anaphylactic patients after emergency treatment.

Contents

List of abbreviations

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
WTP	willingness to pay

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1.0 Introduction

The analysis aimed to inform the following two questions:

What are 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?

1.1 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 [1]. There is little variation in cost and so the cost of AI was based on the BNF 61 cost of Epipen of £26.45, which should be replaced, based on expert opinion, every 12 months.

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)[1].

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.

1.2 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[2], which includes the definition of anaphylaxis. For example, Stewart and Ewan[3] 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[4] 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[5]. However, a more recent study in the UK by Gonzalez-Perez et al[6] 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 [2] 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 [7] 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 [1] 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.

1.3 Systematic review of CEAs

A search stategy was designed in order to retrieve any economic evaluation or cost study in the population of allergy or anaphylaxis (refer to Appendix 1 for how this was applied to each database). 40 papers were retreived from title and abstract screening and 3 met the inlcusion 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 2.

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 vemon anaphylaxis with AI compared to treatment of mild vemon anaphylaxis without AI use	18
Desai and Carroll 2009	DAM	Users of AI	Conventional AI (EpiPen compared to a new AI device (intellijject)	5 (congress abstract)

Table 1: summary of economic evaluations on anaphylaxis
**CEA= cost-effectiveness analysis, DAM= decision analytic model, AI=auto-injector

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 were 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 (Intellijject) 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 (Intellijject, 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.

2.0 Methods

2.1 General approach

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.

2.2 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 5 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 1~~Figure 1~~). 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).

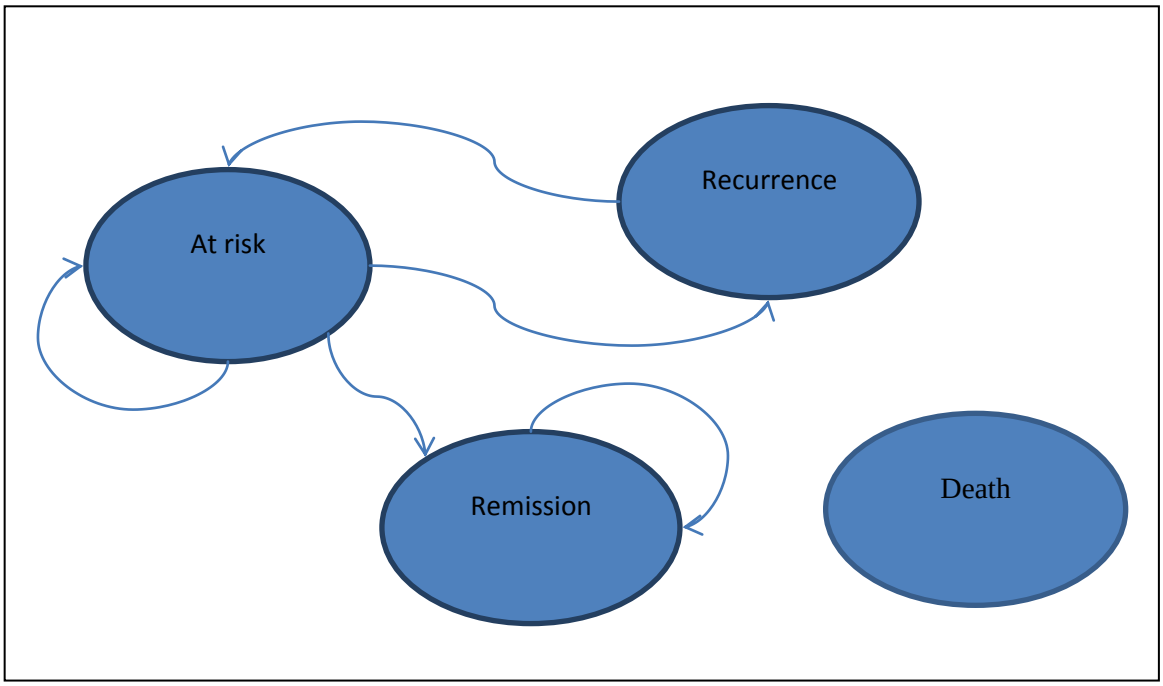

Figure 1: diagram showing the health states and transitions between them: transitions can occur from any live state to the death state.

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 initital '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.

2.3 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 opinon, 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 [4]. 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.

2.4 Model parameters

All parameter values were estimated using the best evidence available and according to best practice [9, 15]. 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 [1, 16-18]. 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) [19], 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 [20]. 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 3.

2.4.1 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 2: population characteristics

2.4.2 Rate of recurrence

	Parameter	Name parameter in model	Distribution type	Min	Most likely	Max	Sources
3	annual rate of recurrence of anayphylaxis due to drugs with SS	dprecurdrugSS	Triangular	0	0.001	0.002	EO*
4	annual rate of recurrence of anayphylaxis due to food with SS	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 anayphylaxis due to food with SC	drecurfood	Triangular	0.05	0.11	0.16	EO* and based on Mullins 2003, Figure 1, page 1037 (see table 2)
6	annual rate of recurrence of idiopathic anayphylaxis with SC	drecuridio	Triangular	0.05	0.28	0.51	EO* and based on Mullins 2003, Figure 1, page 1037 (see table 2)
7	annual rate of recurrence of anayphylaxis due to drugs with SC	drecurdrug	Triangular	0.05	0.12	0.19	EO* and based on Mullins 2003, Figure 1, page 1037 (see table 2)
8	annual rate of recurrence of anayphylaxis due to insect sting with SC	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''

Table 3: 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) [21]. 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) [22]. 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 4~~Table 2~~).

	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 4: 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) [6] 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.

2.4.3 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 5: 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) [23] 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)[6]. There was some expert opinion that the probability of idiopathic in adults would be much higher than in children. However, it was not possible to confirm this based on the available evidence. For example, according to a review of about 2323 cases from the HES between 1991 and 1995, the proportions without aetiology were about 27% for children and 35% for adults [24]. Similarly, a survey of 816 cases of emergency call-outs from ambulance service records in North West

England between 2007 and 2008 revealed allergen not documented in 39% and 40% of cases for children and adults respectively [25]. Of course, these cases then might turn out to have an identifiable trigger, but this should equally apply to children and adults and in the absence of better evidence, it was assumed there was no difference between children and adults.

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 .

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	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 5~~Table 4~~ gives a description of the model inputs, which imply the following marginal probabilities (r/all anaphylaxis=r/343): idiopathic: 30.03%; insect: 13.41%; food: 44.21% (children), 12.51% (adults) and drug: 12.35% (children), 44.05% (adults).

2.4.4 Mortality

	Parameter	Name of	Distribution	n	r	Sources

		parameter in model	type			
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 6: 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)[1]. 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 [1] does contain this data for food, drug (oral

and injected (although only oral used since injected most likely to be administered in a heatlh 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 7~~Table 6~~.

	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 7: 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 8~~Table 7~~.

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 8: 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 9~~Table 8~~.

	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 9: 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 10~~Table 9~~.

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 10: 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:

$Propnot_{amb}$= propnot (2.1-4.5 mins) + propnot (4.6-9.9 mins) + propnot (10-20 mins) + propnot (>20 mins)

Where $propnot_{amb}$ 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:

$Propnot_{amb}$ =propdie (2.1-4.5 mins) + ((1-(propresp(<8 mins)*0.5))*propdie (4.6-9.9 mins)

+ ((1-propresp (<8 mins) - (propresp(8-18 mins) *0.5))* propdie (10-20 mins))

+ (1-propresp(<8 mins) – propresp (8-18 mins) - (propresp (>18)*0.5 mins)) *propdie (>20 mins))

Where propdie is the proportion who die in each time period, shown in Table 8~~Table 8~~ and propresp is the proportion who respond within that time period, shown in Table 10~~Table 10~~. It can be seen that propnot (2.1-4.5 mins)=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:

$Propnot_{amb}$ =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

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:

$Propnot_{amb+AI}$ = $propnot_{amb}$ (2.1-4.5) + ($propnot_{amb}$ (4.6-9.9) * Pcorrect * 0.5)

+ ($propnot_{amb}$ (10-20) * Pcorrect) + (propnot (>20) * Pcorrect)

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

$Ppropnot_{amb+AI}$ = 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, Pdeath, use:

Pdeath = Nno intervention / Nanaphylaxis (1)

Nintervention = pintervention * Nno intervention (2)

Where Nintervention is the number of deaths with current service and AI use, which is 20 (see above, table 5); pintervention is the proportion of deaths not saved, which was calculated to be 0.087852 and Nno intervention is the number of deaths that would have occurred and Nanaphylaxis is the number of cases of anaphylaxis, which is 3517 (see above).

Substituting (2) into (1) gives:

Pdeath =Nintervention / $Propnot_{amb+AI}$ / Nanaphylaxis

=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:

PdeathnoAI =$Propnot_{amb}$* Pdeath

=0.129472 * 0.064729

=0.008381, which would result in 3517*0.008381=about 29 deaths per year.

Pdeath noAI is the probability of death used in the model for no injector use. This means that Pdeath AI is the probability of death with correct AI use (recall that those deaths 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%:

PdeathAI100% =0.00389 * 0.064729

=0.000252, which would result in 3517 * 0.000252 = 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, Pdeath is calculated by using Pcorrect from Capps et al 2010 [25] of 53/116 (about 44%) (see Table 11~~Table 10~~)

	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 11: model parameter for current probability of correct use of AI used only to calculate underlying probability of death due to anaphylaxis, Pdeath (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 12~~Table 11~~).

	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 12: 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 13~~Table 11~~). This makes the estimate more conservative.

	Parameter	Name parameter in model	Distribution type	Min	Most likely	Max	Sources
22	probability use injector correctly with SS	dpinjectorSS	Triangular	0.8	0.9	1	assumption

Table 13: model parameters for probability of correct use of AI with SS

2.4.5 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 14~~Table 13~~ 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 14: 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 15~~Table 14~~)

	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 15: 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 Kransick et al [30], which use the same definition of frequent as the guideline, shown in Table 16~~Table 15~~.

	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 16: proportion of idiopathic patients that have frequent recurrence

2.4.6 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 17: 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).

2.4.7 Utilities

	Parameter	Name of parameter in model	Distribution type	Low	Most likely	High	Sources
29	Utility decrement due to at risk	duatrisk	Triangular	0.06	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 18: 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 no obtained using the EQ-5D instrument, but appeared to be based on an assumption. Indeed the mean length of hospital stay reported in the HES (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).

2.4.8 Costs

	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	£26.45	n/a	BNF 61
35	Costs of two SS sessions (each about £200)	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 maintenance treatment	cVITmaintenance	n/a	n/a	£60	n/a	BNF 61
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 18: cost parameters

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

Table 18 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) [35] 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 (Diwakar 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).

3.0 Results

3.1 Base case results

An arbitrary age of 30 was chosen for the base case and the

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 19~~Table 19~~ and Figure 2~~Figure 2~~ 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 19: base case results (probabilistic)

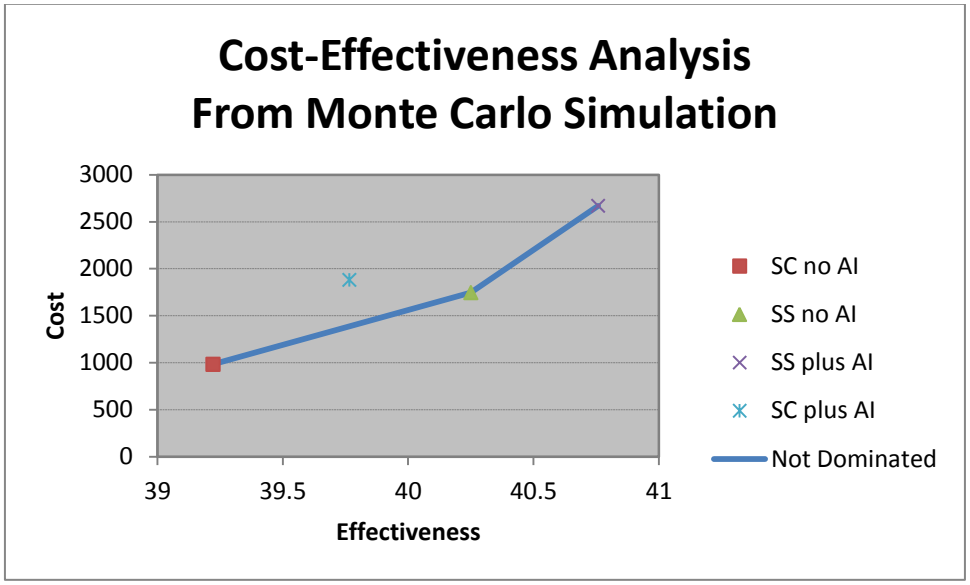

Figure 2: base case results (probabilistic)

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:

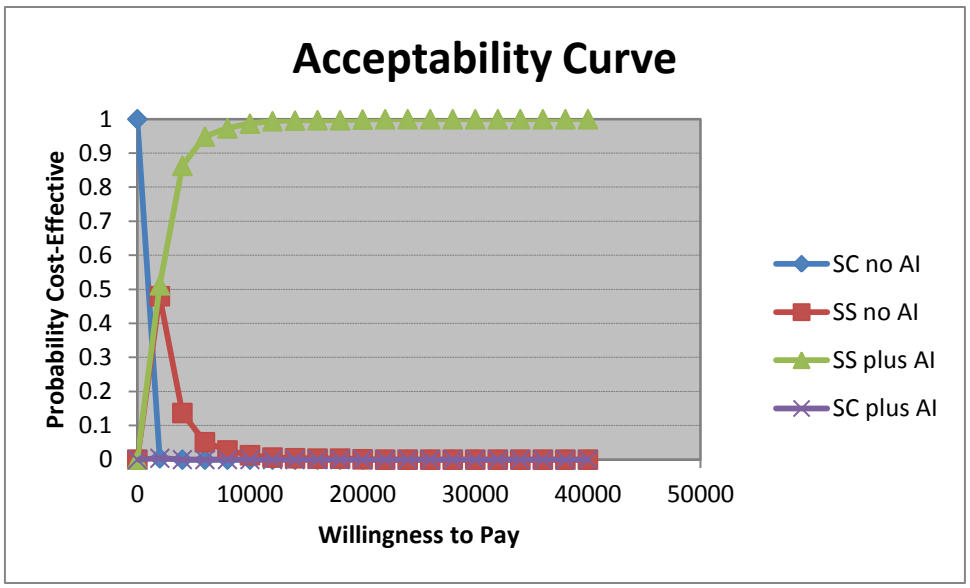

Figure 3: CEAC: base case

Figure 3~~Figure 3~~ 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 20: 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.

3.2 Sensitivity analysis

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 21~~Table 21~~ 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 21: 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).

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	830.21	576.38	1.93	0.02	430.79	26689.05

AI						

Table 22~~Table 22~~ 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 22: 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.

4.0 Discussion

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.

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 [36]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 [6] to be about 30%, but this did not differentiate by age. Two other UK studies were found that did differentiate cause by age [4, 24, 25], 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 [24] and 'allergen not documented' 40% for both adults and children in the other [25]. Also, variation of this proportion by itself had no effective 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.

5.0 Summary

Anaphylaxis is a life-threatening condition that can be caused by a number of different triggers, the main ones being food, insect and drug, but with a large percentage of cases being idiopathic. Both UK and international guidelines recommend both referral to specialist service (SS) for elucidation of trigger and management and prescription of adrenaline injectors (AIs) in case of recurrence. The purpose of this study was to estimate the cost effectiveness of SS and AIs compared to SC (no referral to specialist service) and no AI prescription. Therefore, a Markov type model was constructed, according to best practice, to simulate the natural history and various care pathways for each of the triggers in order to estimate the lifetime NHS cost and QALYs for each of the comparators (SS plus AI, SS no AI, SC plus AI, SC no AI). Evidence to inform model parameters was obtained as systematically as possible, using expert opinion either to validate or provide estimates. Results showed that both SC strategies were dominated (less effective and more costly than SS) and that the ICER for SS plus AI was £1800 with a probability of being cost effective of at least 50% above an ICER threshold of about £2000. This was shown to be robust to extensive sensitivity analysis.

6.0 References

1. Soar, J., et al., *Emergency treatment of anaphylactic reactions--Guidelines for healthcare providers.* Resuscitation, 2008. **77**(2): p. 157-169.
2. Erlewyn-Lajeunesse, M., 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): p. 57-64.
3. Stewart, A.G. and P.W. Ewan, *The incidence, aetiology and management of anaphylaxis presenting to an Accident and Emergency department.* Qjm-Monthly Journal of the Association of Physicians, 1996. **89**(11): p. 859-864.
4. El-Shanawany, T., et al., *Patients with anaphylaxis in accident and emergency are not referred to specialised allergy services.* Journal of Clinical Pathology, 2010. **63**(4): p. 375-375.
5. Sheikh, A., et al., *Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England.* Journal of the Royal Society of Medicine, 2008. **101**(3): p. 139-43.
6. Gonzalez-Perez, A., et al., *Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review.* Journal of Allergy & Clinical Immunology, 2010. **125**(5): p. 1098-1104.e1.
7. Brown, S.G.A., *Clinical features and severity grading of anaphylaxis.* Journal of Allergy and Clinical Immunology, 2004. **114**(2): p. 371-376.
8. Drummond, M.F., et al., *Methods for the Economic Evaluation of Health care programmes*. Oxford medical Publications1997, Oxford: Oxford University press.
9. National Institute for Health and Clinical Excellence, *Guide to the methods of technology appraisal*, 2008, National Institute for Health and Clinical Excellence: London.
10. Briggs, A. and M. Sculpher, *An introduction to Markov modelling for economic evaluation.* Pharmacoeconomics, 1998. **13**(4): p. 397-409.
11. Simons, F.E.R., et al., *World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis.* Journal of Allergy and Clinical Immunology, 2011. **127**(3).
12. Lieberman, P., et al., *The diagnosis and management of anaphylaxis practice parameter: 2010 Update.* Journal of Allergy and Clinical Immunology, 2010. **126**(3).
13. Office for National Statistics. *England and Wales interim lifetables*. 2011; Available from: http://www.statistics.gov.uk/StatBase/Product.asp?vlnk=14459.
14. Cox, L., et al., *Allergen immunotherapy: A practice parameter third update.* Journal of Allergy and Clinical Immunology, 2011. **127**(1).
15. Philips, Z., et al., *Review of guidelines for good practice in decision-analytic modelling in health technology assessment.* Health Technology Assessment, 2004. **8**(36).
16. Simons, F.E.R., *Epinephrine auto-injectors: First-aid treatment still out of reach for many at risk of anaphylaxis in the community.* Annals of Allergy, Asthma and Immunology, 2009. **102**(5): p. 403-409.
17. Simons, K.J. and F.E.R. Simons, *Epinephrine and its use in anaphylaxis: current issues.* Current Opinion in Allergy and Clinical Immunology, 2010. **10**(4): p. 354-361.
18. Simpson, C.R. and A. Sheikh, *Adrenaline is first line treatment for the emergency treatment of anaphylaxis.* Resuscitation, 2010. **81**(6): p. 641-642.
19. Claxton, K., et al., *Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra.* Health Economics, 2005. **14**(4): p. 339-347.
20. Briggs, A., *Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty.* Value Health, 2005. **8**: p. 1 - 2.

21. Ewan, P.W. and A.T. Clark, *Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan.* Lancet, 2001. **357**(9250): p. 111-115.
22. Mullins, R.J., *Anaphylaxis: risk factors for recurrence.* Clinical and Experimental Allergy, 2003. **33**(8): p. 1033-1040.
23. Sampson, H.A., et al., *Symposium on the definition and management of anaphylaxis: summary report.* The Journal of allergy and clinical immunology, 2005. **115**(3): p. 584-91.
24. Alves, B. and A. Sheikh, *Age specific aetiology of anaphylaxis.* Archives of Disease in Childhood, 2001. **85**(4): p. 349-349.
25. Capps, J.A., V. Sharma, and P.D. Arkwright, *Prevalence, outcome and pre-hospital management of anaphylaxis by first aiders and paramedical ambulance staff in Manchester, UK.* Resuscitation, 2010. **81**(6): p. 653-657.
26. Pumphrey, *Lessons for management of anaphylaxis from a study of fatal reactions.* Clinical & Experimental Allergy, 2000. **30**(8): p. 1144-1150.
27. Pumphrey, R.S.H. and M.H. Gowland, *Further fatal allergic reactions to food in the United Kingdom, 1999-2006.* Journal of Allergy and Clinical Immunology, 2007. **119**(4): p. 1018-1019.
28. Pumphrey, R.S.H. and I.S.D. Roberts, *Postmortem findings after fatal anaphylactic reactions.* Journal of Clinical Pathology, 2000. **53**(4): p. 273-276.
29. NHS Information Centre, *Ambulance services England 2008 to 2009*, 2010, NHS: London.
30. Krasnick, J., R. Patterson, and K.E. Harris, *Idiopathic anaphylaxis: Long-term follow-up, cost, and outlook.* ALLERGY, 1996. **51**(10): p. 724-731.
31. Krishna, M.T. and A.P. Huissoon, *Clinical immunology review series: an approach to desensitization.* Clinical & Experimental Immunology, 2011. **163**(2): p. 131-146.
32. Sullivan, P.W. and V. Ghushchyan, *Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States.* Medical Decision Making, 2006. **26**: p. 410-420.
33. Voordouw, J., et al., *Household costs associated with food allergy: an exploratory study.* British Food Journal, 2010. **112**(10-11): p. 1205-1215.
34. Department of Health. *NHS Reference Costs*. 2010 [cited 30/09/2010; Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591.
35. Diwakar, L., et al., *Practice of venom immunotherapy in the United Kingdom: a national audit and review of literature.* Clinical & Experimental Allergy, 2008. **38**(10): p. 1651-1658.
36. Shaker, M.S., *An economic evaluation of prophylactic self-injectable epinephrine to prevent fatalities in children with mild venom anaphylaxis.* Annals of Allergy Asthma & Immunology, 2007. **99**(5): p. 424-428.

Appendix 1: Search strategy

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: 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	no	no	no

given			
(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 3: 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 SS**	dprecurdrugSS	Triangular	0	0.001	0.002	EO*
4	annual rate of recurrence of anaphylaxis due to food with SS	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 SC***	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 SC	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 SC	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 SC	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'')

*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 time, Category B	dtime19B	Beta		2,559,126	2,322,793	**NHS Information Centre 2010**

*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 SC*	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 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))
22	probability use injector correctly with SS **	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	duAIimprove	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 prednisolone	dstartduration	Uniform			1	n/a	2	**Simons et al 2010, Lieberman et al 2010**

*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