

# LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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The clinical and cost-effectiveness  
of Pharmalgen® for the treatment  
of bee and wasp venom allergy



## **1 TITLE OF PROJECT**

The clinical and cost effectiveness of Pharmedgen<sup>®</sup> for the treatment of bee and wasp venom allergy

## **2 TAR TEAM**

Liverpool Reviews and Implementation Group (LRiG), University of Liverpool

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For details of expertise within the TAR team, see section 7.

### **3 PLAIN ENGLISH SUMMARY**

Allergic reactions to bee and wasp venom may occur in venom-sensitive patients immediately following a sting, and can vary in severity, with initially mild symptoms sometimes progressing to critical conditions within seconds. The most severe systemic allergic reactions (generalised reactions) are known as anaphylaxis, a reaction characterised by abnormally low blood pressure, fainting or collapse, and in extreme reactions these symptoms can cause death.

Each year in the UK there are between two and nine deaths from anaphylaxis caused by bee and wasp venom. The immediate treatment for severe allergic reactions to bee and wasp venom consists of emergency treatment with drugs to decrease the patient's response to the venom and support breathing, if required.

To avoid further reactions, the use of sensitisation to bee and wasp venom, through a process known as venom immunotherapy (VIT), has been investigated. Venom immunotherapy consists of subcutaneous injections of increasing amounts of venom into patients with a history of anaphylaxis to bee and wasp venom. Pharmalgen<sup>®</sup> has had UK marketing authorisation for the diagnosis and treatment (using VIT) of allergy to bee venom (using Pharmalgen<sup>®</sup> Bee Venom) and wasp venom (using Pharmalgen<sup>®</sup> Wasp Venom) since March 1995, and it is used by more than 40 centres across the UK. This review aims to assess whether using Pharmalgen<sup>®</sup> in VIT is clinically useful when treating people with a history of severe reaction to bee and wasp stings. The review will compare preventative treatment with Pharmalgen<sup>®</sup> to other treatment options, including high dose antihistamines, advice on the avoidance of bee and wasp stings and adrenaline auto-injector prescription and training. If suitable data are available, the review will also consider the cost effectiveness of using Pharmalgen<sup>®</sup> for VIT and other subgroups including children and people at high risk of future stings or severe allergic reactions to future stings.

## 4 DECISION PROBLEM

### 4.1 Clarification of research question and scope

Pharmalgen® is used for the diagnosis and treatment of immunoglobulin E (IgE)-mediated allergy to bee and wasp venom. The aim of this report is to assess whether the use of Pharmalgen® is of clinical value when providing VIT to individuals with a history of severe reaction to bee and wasp venom and whether doing so would be considered cost effective compared with alternative treatment options available in the NHS.

### 4.2 Background

Bees and wasps form part of the order *Hymenoptera* (which also includes ants), and within this order the species that cause the most frequent allergic reactions are the *Vespidae* (wasps, yellow jackets and hornets), and the *Apinae* (honeybees).<sup>1</sup>

Bee and wasp stings contain allergenic proteins. In wasps, these are predominantly phospholipase A1,<sup>2</sup> hyaluronidase<sup>2</sup> and antigen 5,<sup>3</sup> and in bees are phospholipase A2 and hyaluronidase.<sup>4</sup> Following an initial sting, a type 1 hypersensitivity reaction may occur in some individuals which produces the IgE antibody. This sensitises cells to the allergen, and any subsequent exposure to the allergen may cause the allergen to bind to the IgE molecules, which results in an allergic reaction.

These allergens typically produce an intense, burning pain followed by erythema (redness) and a small area of oedema (swelling) at the site of the sting. The symptoms produced following a sting can be classified into non-allergic reactions, such as local reactions, and allergic reactions, such as extensive local reactions, anaphylactic systemic reactions and delayed systemic reactions.<sup>5-6</sup> Systemic allergic reactions may occur in venom-sensitive patients immediately following a sting,<sup>7</sup> and can vary in severity, with initially mild symptoms sometimes progressing to critical conditions within seconds.<sup>1</sup>

The most severe systemic allergic reaction is known as anaphylaxis. Anaphylactic reactions are of rapid onset (typically up to 15 minutes post sting) and can manifest in different ways. Initial symptoms are usually cutaneous followed by hypotension, with light-headedness, fainting or collapse. Some people develop respiratory symptoms due to an asthma-like response or laryngeal oedema. In severe reactions, hypotension, circulatory disturbances, and breathing difficulty can progress to fatal cardio-respiratory arrest.

Anaphylaxis occurs more commonly in males and in people under 20 years of age and can be severe and potentially fatal.<sup>8</sup>

### 4.3 Epidemiology

It is estimated that the prevalence of wasp and bee sting allergy is between 0.4% and 3.3%.<sup>9</sup> The incidence of systemic reactions to wasp and bee venom is not reliably known, but estimates range from 0.15-3.3%,<sup>10-11</sup> Systemic allergic reactions are reported by up to 3% of adults, and almost 1% of children have a medical history of severe sting reactions.<sup>9, 12</sup> After a large local reaction, 5–15% of people will go on to develop a systemic reaction when next stung.<sup>13</sup> In people with a mild systemic reaction, the risk of subsequent systemic reactions is thought to be about 18%.<sup>13</sup> *Hymenoptera* venom are one of the three main causes of fatal anaphylaxis in the USA and UK.<sup>14-15</sup> Insect stings are the second most frequent cause of anaphylaxis outside of medical settings.<sup>16</sup> Between two and nine people in the UK die each year as a result of anaphylaxis due to reactions to wasp and bee stings.<sup>17</sup> Once an individual has experienced an anaphylactic reaction, the risk of having a recurrent episode has been estimated to be between 60% and 79%.<sup>13</sup>

In 2000, the register of fatal anaphylactic reactions in the UK from 1992 onwards was reported by Pumphrey to determine the frequency at which classic manifestations of fatal anaphylaxis are present.<sup>18</sup> Of the 56 post-mortems carried out, 19 deaths were recorded as reactions to *Hymenoptera* venom (33.9%). A retrospective study in 2004 examined all deaths from anaphylaxis in the UK between 1992 and 2001, and estimated 22.19% to be reactions to *Hymenoptera* venom (47/212). This further breaks down into 29/212 (13.68%) as reactions to wasp stings, and 4/212 (1.89%) as reactions to bee stings. The remaining 14/212 were unidentified *Hymenoptera* stings (6.62%).<sup>19</sup>

### 4.4 Current diagnostic options

Currently, individuals can be tested to determine if they are at risk of systemic reactions to bee and wasp venom. The primary diagnostic method for systemic reactions to bee and/or wasp stings is venom skin testing.

Skin testing involves intradermal injection with the five *Hymenoptera* venom protein extracts, with venom concentrations in the range of 0.001 to 1.0 µg/ml. This establishes the minimum concentration giving a positive result (a reaction occurring in the individual). As venom tests show unexplained variability over time,<sup>20</sup> and as negative skin tests can occur following recent anaphylaxis, it is recommended that tests be repeated after 1 to 6 months.<sup>21</sup>

Other methods of diagnosis in patients following an anaphylactic reaction include radioallergosorbent test (RAST), which detects allergen-specific IgE antibodies in serum. This test is less sensitive than skin testing but is useful when skin tests cannot be done, for example in patients with skin conditions.<sup>22-23</sup>

#### **4.5 Current treatment options**

Preventative treatments include education on how to avoid bee and wasp venom, and prescription of high dose antihistamines. Patients with a history of moderate local reactions should be provided with an emergency kit,<sup>24</sup> containing a H1-blocking antihistamine and a topical corticosteroid for immediate use following a sting. Patients with a history of anaphylaxis should be provided with an emergency kit containing a rapid-acting H1-blocking antihistamine, an oral corticosteroid and an auto-injector for self administration, containing epinephrine.

Injected epinephrine (a sympathomimetic drug which acts on both alpha and beta receptors) is regarded as the emergency treatment of choice for cases of acute anaphylaxis as a result of *Hymenoptera* stings.<sup>25</sup> For adults, the recommended dose is between 0.30 mg/ml and 0.50 mg/ml I.M, and 0.01 ml/kg I.M. for children. Individuals with a history of anaphylactic reactions are recommended to carry auto injectors containing epinephrine (commonly known as EpiPen<sup>®</sup>, Adrenaclick<sup>®</sup>, Anapen<sup>®</sup> or Twinject<sup>®</sup>). These are intended for immediate self-administration by individuals with a history of hypersensitivity to *Hymenoptera* stings and other allergens.

Preventive measures following successful treatment of a systemic allergic reaction to *Hymenoptera* venom consists of either allergen avoidance or specific allergen immunotherapy, known as VIT. Venom immunotherapy is considered to be a safe and effective treatment.<sup>26</sup> Currently, VIT can be used with several regimes, including Pharmalgen<sup>®</sup> (manufactured by ALK Abello, and licensed in the UK), Aquagen<sup>®</sup> and Alutard SQ<sup>®</sup> (both manufactured by ALK Abello and unlicensed in the UK but licensed in some parts of Europe), VENOMENHAL<sup>®</sup> (HAL Allergy, Leiden, Netherlands, unlicensed in the UK), Alyostal<sup>®</sup> (Stallergenes, Antony Cedex, France, unlicensed in the UK), and Venomil<sup>®</sup> (Hollister-Stier Laboratories LLC, unlicensed in the UK). Venom immunotherapy is recommended to prevent future systemic reactions. It is recommended that VIT is considered ‘when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure’.<sup>27</sup> Venom immunotherapy consists of subcutaneous injections of increasing amounts of venom, and treatment is divided into two periods: the build up phase and maintenance phase. Venom immunotherapy is now the standard therapy for *Hymenoptera* sting allergy,<sup>28</sup> and is a model for allergen-specific therapy,<sup>29-30</sup> with success rates (patients who will remain anaphylaxis free) being reported as more than 98% in some studies.<sup>4, 31</sup> There are now 44 centres across the UK which provide VIT to people for bee and wasp sting allergy. Venom immunotherapy is normally discontinued after 3 to 5 years, but modifications may be necessary when treating people with intense allergen exposure (such as beekeepers) or those with individual risk factors for severe reactions. There is no method of assessing which patients will be at risk of further anaphylactic reactions following administration of VIT and those who will remain anaphylaxis free in the long term following VIT.<sup>27</sup>

Local or systemic adverse reactions may occur as a result of VIT. They normally develop within 30 minutes of the injection. Each patient is monitored closely following each injection to check for adverse reactions. Progression to an increased dose only occurs if the previous dose is fully tolerated.

#### **4.6 The technology**

Pharmalgen<sup>®</sup> is produced by ALK Abello, and has had UK marketing authorisation for the diagnosis (using skin testing/intracutaneous testing) and treatment (using VIT) of IgE-mediated allergy to bee venom (Pharmalgen<sup>®</sup> Bee Venom) and wasp venom (Pharmalgen<sup>®</sup> Wasp Venom) since March 1995 (marketing authorisation number PL 10085/0004). The active ingredient is partially purified freeze dried *Vespula spp.* venom in Pharmalgen<sup>®</sup> Wasp Venom and freeze dried *Apis mellifera* venom in Pharmalgen<sup>®</sup> Bee Venom, each provided in powder form for solution for injection.

Before treatment is considered, allergy to bee or wasp venom must be confirmed by case history and diagnosis. Treatment with Pharmedgen® Bee or Wasp Venom is performed by subcutaneous injections. The treatment is carried out in two phases: the initial phase and the maintenance phase.

In the build up phase, the dose is increased stepwise until the maintenance dose (the maximum tolerable dose before an allergic reaction) is achieved. ALK Abello recommends the following dosage proposals: conventional, modified rush (clustered) and rush up dosing. In conventional up dosing, the patient receives one injection every 3-7 days. In modified rush (clustered) up dosing, the patient receives 2-4 injections once a week. If necessary this interval may be extended up to two weeks. The 2-4 injections are given with an interval of 30 minutes. In rush up dosing, while being hospitalised the patient receives injections with a 2-hour interval. A maximum of four injections per day may be given in the initial phase.

The build up phase ends when the individual maintenance dose has been attained and the interval between the injections is increased to 2, 3 and 4 weeks. This is called the maintenance phase, and the maintenance dose is then given every 4 weeks for at least 3 years.

Contra-indications to VIT treatment are immunological diseases (e. g. immune complex diseases and immune deficiencies); chronic heart/lung diseases; treatment with  $\beta$ -blockers; severe eczema. Side effects include superficial wheal and flare due to shallow injection; local swelling (which may be immediate or delayed up to 48 hours); mild general reactions such as urticaria, erythema, rhinitis or mild asthma; moderate or severe general reactions such as more severe asthma, angioedema or an anaphylactic reaction with hypotension and respiratory embarrassment; anaphylaxis (often starting with erythema and pruritus, followed by urticaria, angioedema, nasal or pharyngeal congestion, wheezing, dyspnoea, nausea, hypotension, syncope, tachycardia or diarrhoea).<sup>32</sup>

#### **4.7 Objectives of the HTA project**

The aim of this review is to assess the clinical and cost effectiveness of Pharmedgen® in providing immunotherapy to individuals with a history of type 1 IgE-mediated systemic allergic reaction to bee and wasp venom. The review will consider the effectiveness of Pharmedgen® when compared to alternative treatment options available in the NHS, including advice on the avoidance of bee and wasp stings, high dose antihistamines and adrenaline auto-injector prescription and training. The review will also examine the existing health economic evidence and identify the key economic issues related to the use of Pharmedgen® in UK clinical practice. If suitable data are available, an economic model will be developed and



populated to evaluate if the use of Pharmalgen® for the treatment of bee and wasp venom allergy, within its licensed indication, would be a cost effective use of NHS resources.

## **5 METHODS FOR SYNTHESISING CLINICAL EFFECTIVENESS EVIDENCE**

### **5.1 Search strategy**

The major electronic databases including Medline, Embase and The Cochrane Library will be searched for relevant published literature. Information on studies in progress, unpublished research or research reported in the grey literature will be sought by searching a range of relevant databases including National Research Register and Controlled Clinical Trials. A sample of the search strategy to be used for MEDLINE is presented in

Appendix 1.

Bibliographies of previous systematic reviews, retrieved articles and the submissions provided by manufacturers will be searched for further studies.

A database of published and unpublished literature will be assembled from systematic searches of electronic sources, hand searching, contacting manufacturers and consultation with experts in the field. The database will be held in the Endnote X4 software package.

#### **5.1.1 Inclusion criteria**

The inclusion criteria specified in Table 1 will be applied to all studies after screening. The inclusion criteria were selected to reflect the criteria described in the final scope issued by NICE for the review. However, as there is likely to be a limited amount of RCT data, the inclusion criteria of study design may be expanded to include comparative studies and descriptive cohorts.

Table 1: Inclusion criteria

Intervention(s)	Pharmalgen® for the treatment of bee and wasp venom allergy,
Population(s)	People with a history of type 1 IgE-mediated systemic allergic reactions to: wasp venom and/or bee venom
Comparators	Alternative treatment options available in the NHS, without venom immunotherapy including: <ul style="list-style-type: none"> <li>• advice on the avoidance of bee and wasp venom,</li> <li>• high-dose antihistamines,</li> <li>• adrenaline auto-injector prescription and training</li> </ul>
Study design	Randomised controlled trials Systematic reviews
Outcomes	Outcome measures to be considered include: <ul style="list-style-type: none"> <li>• number and severity of type 1 IgE-mediated systemic allergic reactions</li> <li>• mortality</li> <li>• anxiety related to the possibility of future allergic reactions</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life</li> </ul>
Other considerations	If the evidence allows, considerations will be given to subgroups of people, according to their: <ul style="list-style-type: none"> <li>• risk of future stings (as determined, for example, by occupational exposure)</li> <li>• risk of severe allergic reactions to future stings (as determined by such factors as baseline tryptase levels and co-morbidities)</li> <li>• If the evidence allows, the appraisal will consider separately people who have a contraindication to adrenaline.</li> <li>• If the evidence allows, the appraisal will consider children separately.</li> </ul>

Two reviewers will independently screen all titles and abstracts of papers identified in the initial search. Discrepancies will be resolved by consensus and where necessary a third reviewer will be consulted. Studies deemed to be relevant will be obtained and assessed for inclusion. Where studies do not meet the inclusion criteria they will be excluded.

### **5.1.2 Data extraction strategy**

Data relating to study design, findings and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Study details will be extracted using a standardised data extraction form. If time permits, attempts will be made to contact authors for missing data. Data from studies presented in multiple publications will be extracted and reported as a single study with all relevant other publications listed.

### **5.1.3 Quality assessment strategy**

The quality of the clinical-effectiveness studies will be assessed according to criteria based on the CRD's guidance for undertaking reviews in healthcare.<sup>33-34</sup> The quality of the individual clinical-effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and if necessary a third reviewer will be consulted.

### **5.1.4 Methods of analysis/synthesis**

The results of the data extraction and quality assessment for each study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. All summary statistics will be extracted for each outcome and where possible, data will be pooled using a standard meta-analysis.<sup>35</sup> Heterogeneity between the studies will be assessed using the  $I^2$  test.<sup>34</sup> Both fixed and random effects results will be presented as forest plots.

## **6 METHODS FOR SYNTHESISING COST EFFECTIVENESS EVIDENCE**

The economic section of the report will be presented in two parts. The first will include a standard review of relevant published economic evaluations. If appropriate and data are available, the second will include the development of an economic model. The model will be designed to estimate the cost effectiveness of Pharmedgen® for VIT in individuals with a history of anaphylaxis to bee and wasp venom. This section of the report will also consider budget impact and will take account of available information on current and anticipated patient numbers and service configuration for the treatment of this condition in the NHS.

### **6.1 *Systematic review of published economic literature***

The literature review of economic evidence will identify any relevant published cost-minimisation, cost-effectiveness, cost-utility and/or cost-benefit analyses. Economic evaluations/models included in the manufacturer submission(s) will be included in the review and critiqued as appropriate.

### 6.1.1 Search strategy

The search strategies detailed in section 5 will be adapted accordingly to identify studies examining the cost effectiveness of using Pharmedgen® for VIT in patients with a history of allergic reactions to bee or wasp venom. Other searching activities, including electronic searching of online health economic journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report. The search strategy will be designed to meet the primary objective of identifying economic evaluations for inclusion in the cost-effectiveness literature review. At the same time, the search strategy will be used to identify economic evaluations and other information sources which may include data that can be used to populate a *de novo* economic model where appropriate. Searching will be undertaken in MEDLINE and EMBASE as well as in the Cochrane Library, which includes the NHS Economic Evaluation Database (NHS EED).

### 6.1.2 Inclusion and exclusion

In addition to the inclusion criteria outlined in Table 1, specific criteria required for the cost-effectiveness review are described in Table 2. In particular, only full economic evaluations that compare two or more options and consider both costs and consequences will be included in the review of published literature. Any economic evaluations/models included in the manufacturer submission(s) will be included as appropriate. Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion.

Table 2: Additional inclusion criteria (cost effectiveness)

Study design	Full economic evaluations that consider both costs and consequences (cost-effectiveness analysis, cost-utility analysis, cost-minimisation analysis and cost benefit analysis)
Outcomes	Incremental cost per life year gained Incremental cost per quality adjusted life year gained

### **6.1.3 Data extraction strategy**

Data relating to both study design and quality will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing data. Data from multiple publications will be extracted and reported as a single study.

### **6.1.4 Quality assessment strategy**

The quality of the cost-effectiveness studies/models will be assessed according to a checklist updated from that developed by Drummond et al.<sup>36</sup> This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by NICE.<sup>37</sup> The quality of the individual cost-effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The information will be tabulated and summarised within the text of the report.

## **6.2 Methods of analysis/synthesis**

### **6.2.1 Cost effectiveness review of published literature**

Individual study data and quality assessment will be summarised in structured tables and as a narrative description. Potential effects of study quality will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the manufacturer submission(s) to NICE, will be collated and presented as appropriate.

### **6.2.2 Development of a *de novo* economic model by the AG**

#### *a. Cost data*

The primary perspective for the analysis of cost information will be the NHS. Cost data will therefore focus on the marginal direct health service costs associated with the intervention.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Where possible, unit cost data will be extracted from the literature or obtained from other relevant sources (drug price lists, NHS reference costs and Chartered Institute of Public Finance and Accounting cost databases).

Where appropriate costs will be discounted at 3.5% per annum, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.<sup>37</sup>

#### *b. Assessment of benefits*

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. LRiG anticipates that the main measures of benefit will be increased QALYs.

Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5%, the rate recommended in NICE guidance to manufacturers and sponsors of submissions.<sup>37</sup>

*b. Modelling*

The ability of LRiG to construct an economic model will depend on the data available. Where modelling is appropriate, a summary description of the model and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis (see Section d) will be presented. In addition, LRiG will provide an assessment of the model's strengths and weaknesses and discuss the implications of using different assumptions in the model. Reasons for any major discrepancies between the results obtained from assessment group model and the manufacturer model(s) will be explored.

The time horizon will be a patient's lifetime in order to reflect the chronic nature of the disease.

A formal combination of costs and benefits will also be performed, although the type of economic evaluation will only be chosen in light of the variations in outcome identified from the clinical- effectiveness review evidence.

If data are available, the results will be presented as incremental cost per QALY ratios for each alternative considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost-effectiveness analysis or cost-minimisation analysis will be undertaken. Any failure to meet the reference case will be clearly specified and justified, and the likely implications will, as far as possible, be quantified.

*d. Sensitivity analysis*

If appropriate, sensitivity analysis will be applied to LRiG's model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost-effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making for specific comparisons (e.g. multi-way sensitivity analysis, cost-effectiveness acceptability curves etc).



## **7 HANDLING THE MANUFACTURER SUBMISSION(S)**

All data submitted by the drug manufacturers arriving before 22<sup>nd</sup> March 2011 and meeting the set inclusion criteria will be considered for inclusion in the review. Data arriving after this date will only be considered if time constraints allow. Any economic evaluations included in the manufacturer submission(s) will be assessed. This will include a detailed analysis of the appropriateness of the parametric and structural assumptions involved in any models in the submission and an assessment of how robust the models are to changes in key assumptions. Clarification on specific aspects of the model may be sought from the relevant manufacturer.

Any 'commercial in confidence' data taken from a manufacturer submission will be clearly marked in the NICE report according to established NICE policy and removed from the subsequent submission to the HTA

## **8 EXPERTISE IN THIS TAR TEAM AND COMPETING INTERESTS OF AUTHORS**

This TAR team will be made up of the following individuals:

Team lead /clinical systematic reviewer	Juliet Hockenhull
Senior economic modeller	Professor Adrian Bagust
Systematic reviewer (clinical)	Gemma Cherry
Systematic reviewer (economics)	Dr Angela Boland
Economic modeller	Dr Carlos Martin Saborido
Information specialist	Dr Yenal Dunder
Medical statistician	James Oyee
Director	Ms Rumona Dickson
Clinical advisor	A team of clinical experts will be established to address clinical questions related to the technology and to provide feedback on drafts of the final report

No member of the research team has any competing interests to declare. Any competing interests relating to the external reviewers will be declared in the final report.

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## 1. Appendices

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### Appendix 1 Details of MEDLINE clinical effectiveness search strategies:

1. exp wasps/ or exp bees/
2. \*Hymenoptera/
3. (wasp\$ or honeybee\$ or bees or yellow hornet\$ or yellow jacket\$ or white hornet\$ or poliste\$).tw.
4. \*hypersensitivity, delayed/ or \*hypersensitivity, immediate/
5. ((wasp\$ or bees) adj (venom or sting) adj (hypersensitivit\$ or allerg\$ or anaphylax\$ or systemic reaction\$)).tw.
6. or/1-5
7. Pharmalgen.af.
8. \*Immunotherapy/ or immunotherap\$.ti,ab.
9. \*Desensitization, Immunologic/
10. or/7-9
11. 6 and 10
12. limit 11 to (english language and humans)

## **Appendix 2** Details of economic data extraction and quality assessment

Cost effectiveness data extraction will include, but not be limited to:

- Type of evaluation and synthesis
- Intervention
- Study population/disease
- Time period of study
- Cost items
- Cost data sources
- Country, currency year
- Range of outcomes
- Efficiency data sources
- Modelling method and data sources
- Probabilities and assumptions of models
- Cost effectiveness ratios
- Subgroup analysis and results
- Sensitivity analysis and results
- Authors conclusions

Studies of cost effectiveness will be assessed for quality using the following criteria, which is an updated version of the checklist developed by Drummond:<sup>36</sup>

- Study question
- Selection of alternatives
- Form of evaluation
- Effectiveness data
- Costs
- Benefit measurement and valuation
- Decision modelling
- Discounting
- Allowance for uncertainty
- Presentation and generalisability of results