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A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

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A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

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Abstract

A systematic review of the clinical effectiveness and cost-effectiveness of Pharmalgen® for the treatment of bee and wasp venom allergy

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Background: Each year in the UK, there are between two and nine deaths from anaphylaxis caused by bee and wasp venom. Anaphylactic reactions can occur rapidly following a sting and can progress to a life-threatening condition within minutes. To avoid further reactions in people with a history of anaphylaxis to bee and wasp venom, the use of desensitisation, through a process known as venom immunotherapy (VIT), has been investigated and is in use in the UK. VIT consists of subcutaneous injections of increasing amounts of purified bee and/or wasp venom extract. Pharmalgen® products (ALK Abelló) have had UK marketing authorisation for VIT (as well as diagnosis) of allergy to bee venom (using Pharmalgen Bee Venom) and wasp venom (using Pharmalgen Wasp Venom) since March 1995.

Objective: This review assessed the clinical effectiveness and cost-effectiveness of Pharmalgen in providing immunotherapy to individuals with a history of type 1 [immunoglobulin E (IgE)-mediated] systemic allergic reaction to bee and wasp venom.

Data sources: A comprehensive search strategy using a combination of index terms (e.g. Pharmalgen) and free-text words (e.g. allerg$) was developed and used to interrogate the following electronic databases: EMBASE, MEDLINE, The Cochrane Library.

Review methods: Papers were included if they studied venom immunotherapy using Pharmalgen (PhVIT) in patients who had previously experienced a systemic reaction to a bee and/or a wasp sting. Comparators were any alternative treatment options available in the NHS without VIT. Included outcomes were systemic reactions, local reactions, mortality, anxiety related to the possibility of future allergic reactions, health-related quality of life (QoL) and adverse reactions (ARs) to treatment. Cost-effectiveness outcomes included cost per quality-adjusted life-years (QALYs) gained. Because of the small number of published randomised controlled trials (RCTs), no meta-analyses were conducted. A de novo economic model was developed to assess the cost-effectiveness of PhVIT plus high-dose antihistamine (HDA) plus adrenaline auto-injector (AAI) plus avoidance advice in relation to two comparators.

Results: A total of 1065 citations were identified, of which 266 full-text papers were obtained. No studies were identified that compared PhVIT with any of the outlined

comparators. When these criteria were widened to include different protocols and types of PhVIT administration, four RCTs and five quasi-experimental studies were identified for inclusion. The quality of included studies was poor, and none was conducted in the UK. Eight studies reported re-sting data (systemic reactions ranged from 0.0% to 36.4%) and ARs (systemic reactions ranged from 0.0% to 38.1% and none was fatal). No included studies reported quality of life. No published economic evidence relevant to the decision problem was identified. The manufacturer of PhVIT did not submit any clinical effectiveness or cost-effectiveness evidence to the National Institute for Health and Clinical Excellence in support of PhVIT. The results of the Assessment Group's (AG) base-case analysis show that the comparison of PhVIT + HDA + AAI versus AAI + HDA yields an incremental cost-effectiveness ratio (ICER) of £18,065,527 per QALY gained; PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £7,627,835 per QALY gained. The results of the sensitivity analyses and scenario analyses showed that the results of the base-case economic evaluation were robust for every plausible change in parameter made. The results of the 'High Risk of Sting Patients' subgroup analysis show that PhVIT + HDA + AAI dominates both AAI + HDA and avoidance advice only (i.e. is less expensive and more effective). The 'VIT Anxiety QoL Improvement' subgroup analysis shows that PhVIT + HDA + AAI versus HDA + AAI has an ICER of £23,868 per QALY gained, and PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £25,661 per QALY gained.

Limitations: This review is limited to the use of Pharmalgen in the treatment of hymenoptera venom allergy and therefore does not assess the effectiveness of VIT in general.

Conclusions: The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor-quality clinical effectiveness research. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable. The results of the AG's de novo economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and with avoidance advice only yields ICERs in the range of £8–20M per QALY gained. Two subgroups ('High Risk of Sting Patients' and 'VIT Anxiety QoL Improvement') were considered in the economic evaluation and the AG concludes that the use of PhVIT + AAI + HDA may be cost-effective in both groups. Future research should focus on clearly identifying groups of patients most likely to benefit from treatment and ensure that clinical practice is focussed on these groups. Furthermore, given the paucity of UK data in this area it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic adverse reactions to VIT, rates of systemic reactions to bee/wasp stings).

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Contents

Glossary

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

Anaphylaxis A severe type 1 hypersensitivity allergic reaction.

Aqueous solution A solution in which water is the solvent.

Cost-effectiveness Cost-effectiveness has numerous meanings; however, for practical purposes it is usually given to mean that the cost per quality-adjusted life-year gained is below a notional willingness-to-pay threshold.

Depot An injection of a pharmacological agent that releases its active compound in a consistent way over a long period of time.

Field sting A sting occurring accidentally.

Hymenoptera An order of stinging insects that includes bees, wasps and ants.

Immunoglobulin E Class of antibody that plays an important role in allergy.

Local reactions Reactions mediated by allergic mechanisms but that involve only the part of the body in contact with the sting site.

Sting challenge A sting purposefully inflicted in a controlled environment.

Systemic allergic reactions Reactions mediated by allergic mechanisms that spread to other organs in the body.

Venom immunotherapy A type of allergic desensitisation therapy for people who are highly susceptible to Hymenoptera venom.

List of abbreviations

AAAAI	American Academy of Allergy, Asthma and Immunology
AAI	adrenaline auto-injector
AG	Assessment Group
AR	adverse reaction
BOT	burden of treatment
CRD	Centre for Reviews and Dissemination
EAACI	European Academy of Allergy and Clinical Immunology
EQ-5D	European Quality of Life-5 Dimensions
FS	field sting
HBV	honey bee venom
HDA	high-dose antihistamine
HES	hospital episode statistics
ICER	incremental cost-effectiveness ratio
IDT	intradermal skin testing
IgE	immunoglobulin E
IgG	immunoglobulin G
ITT	intention to treat
LLR	large local reaction
MCMC	Markov chain Monte Carlo
MTC	mixed-treatment comparison
N/A	not available
NA	not applicable
NICE	National Institute for Health and Clinical Excellence
non-PhVIT	venom immunotherapy using non-Pharmalgen® products
NR	not reported
PhVIT	venom immunotherapy using Pharmalgen® products
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RAST	radioallergosorbent testing
RCT	randomised controlled trial
SC	sting challenge
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
SmPC	summary of product characteristics
SPT	skin prick testing
STAI	State-Trait Anxiety Inventory
VIT	venom immunotherapy
VQLQ	Vespid Allergy Quality of Life Questionnaire
WBE	whole bee extract

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

Executive summary

Background

Each year in the UK there are between two and nine deaths from anaphylaxis caused by bee and wasp venom. Anaphylactic reactions to bee and wasp venom are a medical emergency, necessitating immediate treatment with drugs, oxygen and fluids to decrease the patient's response to the venom and support breathing and circulation.

In venom-sensitive individuals, allergic reactions to bee and wasp venom can occur rapidly following a sting, and vary in severity. Initially mild symptoms can progress to a life-threatening condition within minutes. The most severe systemic (or generalised) allergic reaction is referred to as anaphylaxis, which is characterised by features such as low blood pressure (with fainting or collapse), bronchospasm (asthma-like response) and laryngeal oedema (with constriction of the upper airway).

To avoid further reactions in people with a history of anaphylaxis to bee and wasp venom, the use of desensitisation, through a process known as venom immunotherapy (VIT), has been investigated and is in use in the UK. VIT consists of subcutaneous injections of increasing amounts of purified bee and/or wasp venom extract. Pharmalgen® products (ALK Abelló) have had UK marketing authorisation for VIT (as well as diagnosis) of allergy to bee venom (using Pharmalgen Bee Venom) and wasp venom (using Pharmalgen Wasp Venom) since March 1995. They are used by 44 centres in England and Wales.

Objectives

This review assessed the clinical effectiveness and cost-effectiveness of Pharmalgen in providing immunotherapy to individuals with a history of type 1 (immunoglobulin E-mediated) systemic allergic reaction to bee and wasp venom.

Methods

Three electronic databases were searched for comparative trials and economic evaluations of VIT using Pharmalgen (PhVIT) in the treatment of venom allergy. Outcomes for clinical effectiveness included systemic reactions, local reactions, mortality, anxiety related to the possibility of future allergic reactions, health-related quality of life (QoL) and adverse reactions (ARs) to treatment. Cost-effectiveness outcomes included cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including economic evaluations, applied inclusion criteria to relevant publications and quality assessed the included studies. Where multiple publications of the same study were identified, data were extracted and reported as a single study. The results of the data extraction and quality assessment are summarised in structured tables and as a narrative description. The manufacturer did not provide an evidence submission to the National Institute for Health and Clinical Excellence for this appraisal.

Results

Clinical review

A total of 1065 citations were identified, of which 266 full-text papers were obtained. No studies were identified that compared PhVIT with any comparator outlined in the decision problem [adrenaline auto-injector (AAI) prescription and training, high-dose antihistamines (HDAs) or advice on the avoidance of bee and wasp stings]. The decision problem was widened to include different types of PhVIT (such as subcutaneous vs sublingual) or differing protocols of PhVIT administration. Four randomised controlled trials (RCTs) and five quasi-experimental studies were identified for inclusion in the systematic review.

The quality of the included trials was poor. All trials included in the review were small, with none including more than 65 participants (range 6–65), and all of the studies took place outside the UK. The authors did not describe the method of randomisation used, and there were imbalances in the rate of dropout between arms in all but one study. There was heterogeneity between studies in the outcomes reported, the timing of re-stings, the type and length of treatment and the proportion of people being re-stung. As such, it was not possible to conduct a meta-analysis or mixed-treatment comparison with the available data.

Eight studies reported re-sting data and the rate of systemic reactions ranged from 0.0% to 36.4%. ARs to PhVIT were reported in eight studies. Systemic reactions were reported at rates of between 0.0% and 38.1% and none was fatal. Data were supported by non-comparative studies of PhVIT. Seventeen non-comparative studies of PhVIT reported rates of systemic reactions following re-sting, which ranged from 0.0% to 32.7%, with 12 studies reporting re-sting data before the completion of VIT. Post-VIT systemic reaction rates ranged from 2.0% to 12.5%.

Health-related QoL was not reported in any of the included studies; however, details from two RCTs that used a combination of PhVIT and non-PhVIT indicate that the QoL of people receiving VIT improved more than the QoL of those using an EpiPen® (Mylan Inc.) (test for overall effect: $z = 36.25$, $p < 0.00001$).

In general, clinical evidence suggests that there is a decrease in reactions to stings following PhVIT, but there is no direct evidence related to the comparators included in the scope for this project. PhVIT is associated with ARs, but these are treatable and transient. These ARs are also associated with non-PhVIT, and studies have indicated that they may to some extent be balanced by improvements in QoL.

Economic review

No published economic evidence relevant to the decision problem was identified through the systematic review of cost-effectiveness studies. The manufacturer of PhVIT did not submit any clinical effectiveness or cost-effectiveness evidence to NICE in support of PhVIT. The Assessment Group (AG) developed a de novo economic model designed specifically to compare the cost-effectiveness of PhVIT with currently available NHS treatments. A questionnaire was designed and sent out to the 44 allergy clinics in the UK that provide PhVIT to elicit data for use in the economic model. PhVIT + HDA + AAI were compared with (1) HDA + AAI and (2) avoidance advice only.

In the AG base case, the comparison of PhVIT + HDA + AAI versus AAI + HDA yields an incremental cost-effectiveness ratio (ICER) of £18,065,527 per QALY gained; PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £7,627,835 per QALY gained. The sensitivity analyses and scenario analyses showed that the results of the base-case

economic evaluation were robust for every plausible change in parameter made. Under the base-case assumptions, the incremental cost per QALY gained of PhVIT + AAI + HDA compared with an emergency kit of AAI + HDA is never less than £1M per QALY gained under any scenario or any plausible values for parameters within the model. The ICER falls below £1M only when PhVIT + AAI + HDA is compared with avoidance advice and when the most optimistic scenario for PhVIT + AAI + HDA is considered; this ICER still exceeds £700,000 per QALY gained.

The AG's results for the 'High Risk of Sting Patients' subgroup analysis show that PhVIT + HDA + AAI dominates both AAI + HDA and avoidance advice only (i.e. is less expensive and more effective). The AG's 'VIT Anxiety QoL Improvement' subgroup analysis shows that PhVIT + HDA + AAI versus HDA + AAI has an ICER of £23,868 per QALY gained, and PhVIT + HDA + AAI versus avoidance advice only yields an ICER of £25,661 per QALY gained.

Although the findings of the economic model are considered robust, there are some key weaknesses in the data used to inform the economic model. The AG has identified key gaps in the available clinical effectiveness literature and notes specifically that there is a paucity of clinical effectiveness data from RCTs of PhVIT versus any other comparator. The AG is also concerned that the number of stings in people who have had PhVIT in the UK and the number of bee and/or wasp stings in the general population is not known. The AG considers that the likelihood of death following sting for individuals who are allergic to bee and/or wasp venom and the size of the improvement in utility as a result of PhVIT because of a reduction in anxiety because of reduced risk of sting are uncertain.

Conclusions

The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor-quality clinical effectiveness research.

The AG did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal, that is, a comparison of the use of PhVIT with the alternative treatment options of advice on the avoidance of bee and wasp venom, HDA and/or AAIs.

This lack of evidence and the need to identify data to inform the development of an economic model prompted the AG to broaden the search criteria for the systematic review in order to compare PhVIT with other PhVIT and PhVIT with non-PhVIT, to consider data from non-comparative studies of PhVIT and to examine studies reporting the clinical effectiveness of non-PhVIT.

In general, research in the area is limited to small-scale studies that do not appear to have been carried out using robust methods, and none of the studies reported on the use of PhVIT within the UK. There is also heterogeneity in the published evidence related to the methods of PhVIT administration and length of treatment described in the trials. Therefore, conclusions regarding the clinical effectiveness of PhVIT to reduce the rate of future systemic reactions in patients with a history of bee and/or wasp allergic reaction cannot be drawn with any confidence. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable.

Anxiety related to the possibility of future stings is an issue for debate and data from studies of VIT indicate a small improvement in QoL as a result of a decrease in sting-related anxiety after VIT.

No published research on the cost-effectiveness of PhVIT or non-PhVIT was identified by the literature searches. The results of the AG's de novo base-case economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and compared with avoidance advice only yields ICERs in the range of £8–20M per QALY gained. The results of extensive sensitivity and scenario analyses demonstrate that the base-case results are robust. Two subgroups were considered in the economic evaluation and the AG concludes that use of PhVIT + AAI + HDA may be cost-effective in both groups. In the subgroup of patients at high risk of future stings (five stings per year), PhVIT + AAI + HDA dominates the alternatives. In the subgroup of patients whose QoL improves from reduced anxiety as a result of PhVIT, when PhVIT + AAI + HDA is compared with the alternatives the ICERs are in the range of £25,767–27,504 per QALY gained.

Future research

Use of PhVIT in clinical practice in the UK NHS is commonplace; it is therefore highly unlikely that placebo-controlled studies will ever be carried out. The findings of this review indicate, however, that it is necessary to identify more clearly the groups of patients most likely to benefit from treatment and ensure that clinical practice is focused on these groups. Second, given the paucity of UK data in this area, it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic ARs to VIT, rates of systemic reactions to bee/wasp stings).

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1

Background

Clarification of research question and scope

Pharmalgen® products (ALK Abelló) are used for the diagnosis and treatment of immunoglobulin E (IgE)-mediated allergy to bee and wasp venom. The aim of this systematic review was to assess whether use of Pharmalgen products is of clinical value when providing VIT to individuals with a history of severe reaction to bee and wasp venom, and whether it would be considered cost-effective compared with alternative treatment options available in the NHS in England and Wales.

Description of health problem

Aetiology, pathology and prognosis

Apidae (bees), Vespidae (wasps and hornets) and Formicidiae (ants) form part of the order Hymenoptera. Bees and wasps have a modified ovipositor at the terminal end of their abdomen that gives them the ability to sting other organisms. Bees possess a barbed stinger, which, together with their venom sac, remains in their victim's skin after they sting. This means that bees are able to sting only once, and die soon afterwards. Wasps' stingers are not barbed and they are therefore capable of delivering more than one venom-injecting sting in their lifetime. Bee and wasp stings contain allergenic proteins. In wasps, these are predominantly phospholipase A1,[1] hyaluronidase[1] and antigen 5[2] and, in bees, phospholipase A2 and hyaluronidase.[3] It has been estimated that each bee sting contains 147 µg of venom and each wasp sting contains 17 µg of venom.[4]

The symptoms produced following a sting can be classified into non-allergic and allergic reactions. All envenomated individuals are likely to experience local burning and pain followed by erythema (redness) and a small area of oedema (swelling) at the site of the sting. These are caused by vasoactive components of venom and the mechanism is toxic rather than allergic.[4]

Following an initial sting, some individuals generate an immune response, which produces antibodies of the IgE class. These antibodies sensitise cells, particularly histamine-containing mast cells, so that allergen re-introduced by a subsequent exposure can bind to the preformed IgE molecules, triggering the cells to produce a rapid inflammatory response (this is referred to as a 'type 1' or 'immediate-type' hypersensitivity reaction). These allergic reactions in venom-sensitised individuals can be local or systemic, can vary in severity and are typically of rapid onset.[5–8] The term 'anaphylaxis' is applied to the most severe reactions. These frequently occur within 15 minutes of a sting; initial symptoms are usually cutaneous (flushing, urticaria, angioedema) followed by hypotension (with light-headedness, fainting or collapse) and/or respiratory symptoms (due to an asthma-like response or laryngeal oedema). Progression to fatal cardiorespiratory arrest can occur within several minutes.[5] Anaphylaxis occurs more commonly in males and in people under 20 years of age,[6] and the species that cause the most frequent allergic reactions in humans following a sting are the Apidae (bees) and the Vespidae (wasps and hornets).[7]

In addition to local and systemic allergic reactions, individuals may also experience allergic reactions due to circulating immune complexes or delayed hypersensitivity reaction. This is uncommon, and presents as skin rashes and sickness-like symptoms occurring within 3 days to 2 weeks post sting.[5]

Severity of systemic reactions to Hymenoptera venom can be measured using the Mueller grading system,[8] which is summarised in *Table 1*. The grading system classifies the reaction to a sting according to the severity of symptoms. Severity ranges from grade 1 (symptoms of skin and mucous membranes) to grade 4 (cardiovascular symptoms).

Epidemiology

In the UK, insect stings are the second most frequent cause of anaphylaxis outside of medical settings,[9] and Hymenoptera venoms are one of the three main causes of fatal anaphylaxis in both the USA and the UK.[10] It is estimated that the prevalence of bee and wasp sting allergy is between 0.4% and 3.3%.[11]

The prevalence rates of large local reactions (LLRs) in the general population have been estimated at between 2.4% and 26.4%, and up to 38% in beekeepers.[10] Children are reported to have lower rates of both large local and systemic reactions to Hymenoptera stings, at between 11.5% and 19% and between 0.15% and 0.8%, respectively.[5] After a LLR, 5–15% of people will go on to develop a systemic reaction when next stung.[12]

The prevalence of systemic reactions to Hymenoptera venom is not reliably known, but estimates range from 0.5% to 3.3% in the USA,[12,13] and from 0.3% to 7.5% in Europe.[10] Differences in rates of systemic allergic reactions in children and adults have been reported: up to 3% of adults and almost 1% of children have a medical history of severe sting reactions.[11,13] In people with a mild systemic reaction, the risk of subsequent systemic reactions is thought to be between 14% and 20%.[12] Within the USA, severe life-threatening reactions occur in 0.4–0.8% of children and 3% of adults.[14]

UK data

Between two and nine people in the UK die each year as a result of anaphylaxis due to having experienced reactions to bee and wasp stings.[15] Once an individual has experienced an anaphylactic reaction, the risk of having a recurrent episode has been estimated to be between 60% and 79%.[12] In 2000, the register of fatal anaphylactic reactions in the UK from 1992 to 2000 was reported by Pumphrey and Roberts.[16] Of the 56 postmortems carried out during this period, 19 deaths (33.9%) were recorded as reactions to Hymenoptera venom. A retrospective study in 2004[17] examined all deaths from anaphylaxis in the UK between 1992 and 2001 and estimated 47/212 (22.2%) to have resulted from reactions to Hymenoptera venom during this period.

TABLE 1 Mueller grading system

Grade	Description	Signs and symptoms
1: Slight general reaction	Skin and mucous membrane symptoms	Generalised urticaria or erythema, itching, malaise or anxiety
2: General reaction	Gastrointestinal symptoms	Any of the above plus two or more of generalised oedema, constriction in chest, wheezing, abdominal pain, nausea and vomiting, dizziness
3: Severe general reaction	Respiratory symptoms	Any of the above plus two or more of dyspnoea, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
4: Shock reaction	Cardiovascular symptoms	Any of the above plus two or more of loss of consciousness, incontinence of urine or faeces, cyanosis

This further breaks down into 29/47 (61.7%) from reactions to wasp stings and 4/47 (8.5%) from reactions to bee stings, the remaining 14/47 being caused by unidentified Hymenoptera stings (29.8%).[17]

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 allergic sensitisation to bee and/or wasp stings is venom skin testing.

Venom skin testing involves skin prick testing (SPT) and/or intradermal skin testing (IDT) by injection with Hymenoptera venom protein extracts at concentrations in the range of 0.001–1.0 µg/ml. This establishes the minimum concentration giving a positive result. Guidelines produced by the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the European Academy of Allergy and Clinical Immunology (EAACI)[12,18,19] recommend that SPT be the first line of investigation to diagnose Hymenoptera venom allergy, and be performed 2 weeks after the sting reaction. IDT should be used when the results of SPT are negative, as IDT is 90% more sensitive than SPT at a concentration of 1 µg/ml.[12] As venom tests show unexplained variability over time,[20] and as negative skin tests can occur following recent anaphylaxis, if an individual displays a history of systemic reactions but his or her skin tests are negative it is recommended that tests should be repeated 1–2 months later, along with serum-specific IgE measurement.[12]

Another method of diagnosis is direct measurement of allergen-specific IgE antibodies in serum (previously, and sometimes still, referred to as radioallergosorbent testing, or RAST, although this is now an anachronistic misnomer). This test is less sensitive than a skin test but is useful when skin tests cannot be carried out, for example in people with skin conditions.[21,22]

Current treatment options

For treatment of symptoms in the event of being stung, people can be provided with an emergency kit.[23] The contents can be tailored to the perceived risk of a severe reaction but the options include an H1-blocking high-dose antihistamine (HDA), a corticosteroid, a bronchodilator and an adrenaline auto-injector (AAI).

Injected adrenaline (a sympathomimetic drug that acts on both alpha- and beta-adrenoceptors), administered as part of hospital treatment, is regarded as the emergency treatment of choice for cases of acute anaphylaxis as a result of Hymenoptera stings.[24] For adults, the recommended dose is between 0.3 mg and 0.5 mg via intramuscular injection, and 0.01 mg/kg via intramuscular injection for children. AAIs available in the UK for carriage by individuals at risk of anaphylactic reactions, and designed for immediate self-administration, include EpiPen® (Mylan Inc.) and Anapen® (Lincoln Medical Ltd). These AAIs must be prescribed by a clinician. People and their relatives/carers receive training in using the AAI, and are advised to practise regularly using a suitable training device.[25]

In addition to emergency treatments, preventative measures include education (avoidance advice) on how to avoid bee and/or wasp stings. Additionally, education includes advice on recognising the early symptoms of anaphylaxis so that individuals summon help quickly and are prepared to use their emergency medication. All those at high risk should consider wearing

a device such as a bracelet (e.g. MedicAlert) that provides information about their history of anaphylactic reaction to bee and/or wasp venom.[25]

Venom immunotherapy

In addition to the measures detailed above, people with a history of a systemic allergic reaction to Hymenoptera venom can be considered for specific allergen immunotherapy. It is recommended that venom immunotherapy (VIT) is considered 'when positive test results for specific IgE antibodies correlate with suspected triggers and patient exposure'.[26] VIT is intended to prevent or reduce the severity of future systemic allergic reactions and can be administered using a variety of products and according to a variety of protocols. Currently, the only products licensed for use in the UK are Pharmalgen products (*Table 2*).

Venom immunotherapy consists of subcutaneous injections of increasing amounts of venom, and treatment is divided into two periods: the updosing phase and the maintenance phase. VIT is normally discontinued after 3–5 years, but adjustments to the treatment regime may be necessary when treating people with intense allergen exposure (such as beekeepers) or those with individual risk factors for severe reactions. There are 44 centres across the UK that provide PhVIT to people for bee and wasp sting allergy.[27] From the findings of the latest UK audit,[14] it is clear that there is no single standard approach to the delivery of PhVIT; different centres appear to follow different dosing and administration protocols and every treatment package is tailored to the requirements of the individual patient.

In 1978, the first randomised controlled trial (RCT)[28] assessing the effectiveness of VIT in the treatment of insect venom allergy was published, in which people were randomised to either VIT or placebo. Systemic reactions following re-sting occurred in 7 of 12 people receiving placebo and in 1 of 18 people receiving VIT. As a direct result of this study, it is now considered unethical to randomise people eligible for VIT to receive placebo treatment.

Assessing the effectiveness of venom immunotherapy

The impact of VIT can be assessed using both clinical and psychological outcomes. Clinical outcomes relate to the effectiveness of VIT in reducing the rate of reaction to subsequent stings and the psychological outcomes relate to quality of life (QoL) and anxiety related to fear of future stings.

The effectiveness of VIT has been assessed using various methods. A method frequently used in clinical trials is that of a hospital sting challenge (SC), in which a patient is purposely stung, in a controlled environment, by a living insect of the species to which they have been desensitised. Any reaction to the sting is then reported and treated if necessary. Another measure of

TABLE 2 Venom immunotherapy products

Drug	Manufacturer	Licensed in the UK?
Pharmalgen bee venom	ALK Abelló	Yes
Pharmalgen wasp venom	ALK Abelló	Yes
Aquagen®	ALK Abelló	No
Alutard SQ®	ALK Abelló	No
Alyostal®	Stallergenes	No
VENOMENHAL®	HAL Allergy	No
Venomil®	Hollister-Stier Laboratories LLC	No

effectiveness is that of patient-reported reactions to accidental field stings (FSs). Other methods include the measurement of serum IgE and skin tests similar to those used in the diagnosis of venom allergy. However, there is no completely reliable method of predicting which people will be at risk of further anaphylactic reactions and which will remain anaphylaxis free in the long term, following VIT.[26]

Local or systemic adverse reactions (ARs) may occur as a result of VIT. They normally develop within 30 minutes of the injection, but occasionally delayed reactions can occur after several hours. Each patient is monitored closely following each injection to check for ARs. These reactions inform the rate of progression to increased doses during the updosing phase of treatment.

Relevant national guidelines

Emergency treatment

The Resuscitation Council of the UK updated guidelines for the emergency treatment of anaphylactic reactions in 2008.[25] These guidelines detail the diagnosis, treatment, investigation and follow-up of people who have had an anaphylactic reaction, including those reacting to Hymenoptera venom. Emergency treatment with 0.5 mg of intramuscular adrenaline is recommended for people experiencing an anaphylactic reaction. Intravenous adrenaline is recommended only for occasional use by experienced specialists; subcutaneous or inhaled adrenaline is not recommended. Treatment with the highest concentration of oxygen available via a mask, and loading with 500–1000 ml of fluids (for adults) is also recommended, in addition to adrenaline.

High-dose antihistamines are recommended as a second-line treatment for anaphylaxis to help counter histamine-mediated vasodilatation and bronchoconstriction.[25] For adults, chlorphenamine 10 mg intramuscularly or intravenously is recommended. People experiencing an anaphylactic reaction should be treated and then observed for at least 6 hours in a clinical area with facilities for treating life-threatening breathing complications.

The Resuscitation Council of the UK[25] also recommends that all people presenting with anaphylaxis should be referred to an allergy clinic to determine the cause of the reaction and to prepare the patient to be able to manage future episodes themselves.

Preventative measures

The AAAAI guidelines for the management and prevention of stinging insect hypersensitivity were first produced in 1999,[29] and were subsequently updated in 2004[30] and 2011.[18] They recommend that people who have experienced a systemic reaction to an insect sting should be referred to an allergist–immunologist for skin testing or in vitro testing for venom-specific IgE antibodies. A positive IDT response to insect venom at a concentration of $\leq 1.0\,\mu g/ml$ demonstrates the presence of specific IgE antibodies, and VIT is recommended. If people have a negative skin test despite a history of anaphylaxis, in vitro testing for IgE antibodies or repeat skin testing is recommended before concluding that VIT is not indicated.

Venom immunotherapy in adults is usually recommended for all individuals who have experienced systemic reactions, but is generally not necessary for individuals who have had only an LLR because of low risk of a systemic reaction to a subsequent sting. The AAAAI[18] recommends that, once started, VIT should be continued for at least 3–5 years. During this time, and in people who did not commence VIT, it is recommended that people carry an AAI at all times.

The technology

Pharmalgen products are produced by ALK Abelló and have had UK marketing authorisation for the diagnosis (using skin testing/intracutaneous testing) and treatment (using PhVIT) of IgE-mediated allergy to bee venom (Pharmalgen Bee Venom) and wasp venom (Pharmalgen Wasp Venom) since March 1995 (marketing authorisation number PL 10085/0004).[31] The active ingredient is freeze-dried *Apis mellifera* venom in Pharmalgen bee venom and partially purified, freeze-dried *Vespula* spp. venom in Pharmalgen wasp venom, each provided with a solvent to prepare for injection.

Before treatment is considered, allergy to bee or wasp venom must be confirmed by case history and diagnostic testing as outlined previously. Treatment with Pharmalgen bee or wasp venom is performed by subcutaneous injection. The treatment is carried out in two phases: the updosing phase and the maintenance phase.

In the updosing phase, the dose is increased stepwise until the maintenance dose (the maximum tolerable dose before an allergic reaction, or a maximum dose of 100 µg, whichever is the smaller) is achieved. ALK Abelló recommends the following dosage protocols: 'conventional', 'modified rush' (clustered) and 'rush' updosing. In conventional updosing, the patient receives one injection every 3–7 days. In modified rush (clustered) updosing, the patient receives two to four injections once a week. If necessary, this interval may be extended up to 2 weeks. The two to four injections are given with an interval of 30 minutes. In rush updosing, while hospitalised, the patient receives injections at 2-hour intervals and a maximum of four injections per day may be given in the updosing phase. An ultra-rush protocol has also been used in some studies in which hospitalised patients receive all injections in one day at 30-minute intervals.[32]

The updosing phase ends when the individual maintenance dose has been attained and the interval between the injections is increased by 2, 3 or 4 weeks. This is called the maintenance phase, and the maintenance dose is then given every 4–6 weeks for at least 3 years.

In the UK, treatment is carried out in hospital, either as an outpatient for conventional updosing or as an inpatient for rush protocols. Treatment is administered by a specialist, and emergency resuscitation equipment should be available in case it is required to treat any systemic reaction. Venom from ALK Abelló is used in most clinics in the UK, with 92% of clinics employing the conventional 12-week updosing protocol and the remainder employing a clustered (7- to 8-week) updosing protocol.[14]

For bee venom-sensitised people, the relevant PhVIT preparation costs £54.81 during the updosing phase and then £15.94 per injection during the maintenance phase. For wasp venom-sensitised people, PhVIT costs £67.20 during the updosing phase and then £20.51 per injection during the maintenance phase.

Contraindications/warnings

The Pharmalgen summary of product characteristics (SmPC)[31] lists several contraindications to PhVIT treatment. These are immunological diseases (e.g. immune complex diseases and immune deficiencies), chronic heart/lung diseases, treatment with beta-blockers and severe eczema. Side effects include superficial wheal and flare, local swelling (which may be immediate or delayed up to 48 hours), mild general reactions (urticaria, erythema, rhinitis or mild asthma) and moderate or severe general reactions (more severe asthma, angioedema or anaphylactic reaction with hypotension and respiratory embarrassment and possible death).[31]

Chapter 2

Definition of the decision problem

Decision problem

The remit of this review is to assess the clinical effectiveness and cost-effectiveness of PhVIT in providing immunotherapy to individuals with a history of type 1 IgE-mediated systemic allergic reaction to bee and wasp venom. *Table 3* shows the key elements of the decision problem of the appraisal.

Following completion of the review protocol and preliminary searches, revisions were made to the review protocol so as to include any VIT as a comparator to PhVIT, and comparative studies in addition to RCTs, systematic reviews and economic evaluations. These are reflected in the revised decision problem set out in *Table 3*.

TABLE 3 Key elements of the decision problem

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 bee venom and/or wasp venom
Comparators	Alternative treatment options available in the NHS without VIT including ■ advice on the avoidance of bee and wasp venom ■ HDAs ■ AAI prescription and training Revised inclusion criteria ■ any VIT
Study design	Randomised controlled trials Systematic reviews Economic evaluations Revised inclusion criteria ■ comparative studies
Outcomes	Outcome measures to be considered include ■ number and severity of type 1 IgE-mediated systemic allergic reactions ■ mortality ■ anxiety related to the possibility of future allergic reactions ■ adverse effects of treatment (i.e. ARs) ■ health-related QoL ■ QALYs
Other considerations	If the evidence allows, considerations will be given to subgroups of people according to their ■ risk of future stings (as determined, for example, by occupational exposure) ■ risk of severe allergic reactions to future stings (as determined by such factors as baseline tryptase levels and comorbidities) If the evidence allows, the appraisal will consider ■ people who have a contraindication to adrenaline separately ■ children separately

QALY, quality-adjusted life-year.

This review, for the National Institute for Health and Clinical Excellence (NICE), was limited to Pharmalgen, which is the only licensed venom product for use in VIT in the UK. At the time of writing, a systematic review of all VIT was being undertaken by the Cochrane Skin Group, to be published in 2011.[33] To place the current review in the context of the overall literature on the clinical effectiveness of VIT, the Assessment Group (AG) worked in collaboration with the Cochrane Skin Group to provide the best available summary of the evidence for the use of VIT in the treatment of Hymenoptera allergy.

Overall aims and objectives of assessment

The aim of this review was to assess the clinical effectiveness and cost-effectiveness of Pharmalgen in providing immunotherapy to individuals with a history of type 1 IgE-mediated systemic allergic reaction to bee and wasp venom. The review considered the effectiveness of PhVIT when compared with alternative treatment options available in the NHS, including advice on the avoidance of bee and wasp stings, and HDA and AAI prescription and training. The review also examined the existing health economic evidence and identified the key economic issues related to the use of PhVIT in UK clinical practice and developed a de novo economic model.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The methods used for reviewing both the clinical effectiveness and the cost-effectiveness literature are described in this section.

Search strategy

A comprehensive search strategy using a combination of index terms (e.g. Pharmalgen) and free-text words (e.g. allerg$) was developed and used to interrogate the following electronic databases:

- EMBASE (1980 to 2011 Week 4)
- MEDLINE (1948 to February Week 3 2011)
- The Cochrane Library (February 2011).

The results were entered into an Endnote X4 library (Thomson Reuters, CA, USA) and the references were de-duplicated. Full details of the search strategies and the number of citations returned for each search are presented in *Appendix 1*.

Inclusion and exclusion criteria

The identified citations were assessed for inclusion through two stages and disagreements were resolved through discussion. In stage 1, two reviewers (JH/GC) independently screened all titles and abstracts and identified the potentially relevant articles to be retrieved. In stage 2, full-paper manuscripts of identified studies were assessed independently by two reviewers (JH/GC) for inclusion using the criteria as outlined in the decision problem (*Table 3*) and described below. Studies that did not meet the criteria were excluded from the review and their bibliographic details are listed alongside reasons for their exclusion in *Appendix 2*. Bibliographic details of included studies are shown in *Appendix 3*.

Study design

Any comparative studies were included in the assessment of clinical effectiveness of PhVIT. Full economic evaluations were included in the assessment of cost-effectiveness. The Evidence Review Group also identified and assessed the quality of existing systematic reviews to cross-check for additional studies. A summary and critique of relevant systematic reviews is presented in *Comparative studies of venom immunotherapy other than Pharmalgen*.

Intervention

The use of Pharmalgen within its licensed indication was assessed. Where non-PhVIT was administered and compared with non-VIT interventions, these studies were identified but excluded from the review.

Comparator(s)

All of the studies describing the clinical effectiveness of PhVIT compared with any alternative treatment options available in the NHS without VIT, that is, advice on avoidance of bee and wasp venom or HDA or AAI prescriptions and training, were considered for inclusion. These criteria were later widened to include any comparator to PhVIT, including non-PhVIT and different

PhVIT dosing protocols and administration methods. These changes are reflected in the decision problem in *Table 3*.

Population

To be included studies must have investigated people with a history of type 1 IgE-mediated systemic allergic reactions to bee venom and/or wasp venom determined by a history of a systemic reaction to a sting and a positive skin test and/or positive tests for the detection of serum IgE.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: reaction to subsequent stings (assessed through accidental FS or SC), anxiety related to the possibility of future allergic reactions, reported ARs to treatment and QoL. For the assessment of cost-effectiveness, outcomes considered were incremental cost per quality-adjusted life-year (QALY) gained.

Data abstraction strategy

Data relating to both study design and quality were extracted by one reviewer (JH) into a Microsoft Access 2007 database (Microsoft Corporation, Redmond, WA, USA) and were cross-checked by a second reviewer (GC). Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Critical appraisal strategy

The quality of the included clinical effectiveness studies was assessed by one reviewer (JH) and checked by a second reviewer (GC) according to criteria based on CRD (Centre for Reviews and Dissemination) Report 4.[34] The checklist used to critically appraise the included studies is specific to RCTs; for the non-RCT studies a modified version of this checklist was used. All relevant information was tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical effectiveness studies are reported in *Appendix 4*.

Methods of data synthesis

The results of the data extraction are summarised in structured tables and as a narrative description. A standard meta-analysis was planned if sufficient clinically and statistically homogeneous data were available from the included studies. The primary outcomes identified for our evidence synthesis were systemic reaction to FS or SC during treatment and/or ARs to VIT. Secondary outcomes included LLR to VIT, LLR to FS or SC, number of stings and deaths.

We planned to extract number of events for each outcome and total number of people in each treatment arm in order to calculate odds ratios and the corresponding 95% confidence intervals for each study. Studies with no events in both arms would be excluded from analysis. All analyses were planned based on the intention-to-treat (ITT) population where possible. Where appropriate, the levels of clinical and methodological heterogeneity would be investigated, and statistical heterogeneity would be assessed using Q- and I^2-statistics.[35,36] Given the small number of trials available, a fixed-effects model was planned using the 'metan' command within Stata Version 9.2 (StataCorp LP, College Station, TX, USA) where pooling was appropriate.

If the data allowed, a mixed-treatment comparison (MTC) of relevant comparators to PhVIT would be considered. A MTC analysis allows for the synthesis of data from direct and indirect comparisons, and allows for the ranking of different treatments in order of efficacy and estimation of the relative treatment effect of competing interventions. This approach assumes 'exchangeability' of treatment effect across all included trials, such that the observed treatment effect for any comparison could have been expected to arise if it had been measured in all other

included trials. This approach fulfils the objective of providing simultaneous comparison of all of the relevant treatment alternatives, and can provide information about the associated decision uncertainty or sufficient information for economic evaluation. Hence, for the purposes of decision-making, a Bayesian MTC framework would be adopted to synthesise information on all technologies simultaneously using Markov chain Monte Carlo (MCMC) methods to estimate the posterior distributions for our outcomes of interest. The MCMC simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. As with all meta-analyses, MTC may be conducted using either fixed- or random-effects models. Random-effects models allow for the possibility that the true treatment effect may differ between trials. The model fit will be assessed based on residual deviance and deviance information criteria.

WinBUGS version 1.4 statistical software[37] (MRC Biostatistics Unit, Cambridge, UK) was planned for use in the MTC.[38] Two chains would be used to ensure that model convergence was met after 50,000 iterations with a burn-in of 100,000. Formal convergence of the models would be assessed using trace plots and the Gelman–Rubin approach[39] and through inspection of the history plots.

Data would be pooled only if it was felt that the studies were measuring the same effects and if the studies had the same study design. When meta-analysis was considered unsuitable for the data that were identified (e.g. because of the heterogeneity of the studies, or because no reliable data were presented in the report), a narrative synthesis approach would be employed.

Results

Quantity and quality of research available

The electronic searches identified 1397 citations, which, after de-duplication, included 1065 individual papers, of which 799 were excluded after scanning titles and abstracts in stage 1. The full papers of 266 references were obtained and screened using the previously described inclusion criteria. Of the 266 papers screened at stage 2, 11 papers (nine studies) met the revised inclusion criteria. Of the remaining 255 excluded papers, the majority (161) were not comparative studies of PhVIT; other reasons for exclusion included inappropriate outcomes and irrelevant patient populations (*Figure 1*).

There were 38 excluded papers that require further mention in this report as they met the majority of the inclusion criteria but were studies of non-PhVIT. These 38 papers included 16 papers that compared two non-PhVIT treatments and 12 papers that compared non-PhVIT with no VIT [placebo, AAI prescriptions or whole bee extract (WBE)] and are described in the clinical effectiveness section (see *Comparative studies of venom immunotherapy other than Pharmalgen*). Seven papers provided data on QoL and three were economic papers (see *Figure 1*).

Nine comparative studies, reported in 11 publications,[32,40–49] met the inclusion criteria for this review. The references discussed in the text refer to the primary papers and any other publications of the study are listed by study in *Appendix 3*. A summary of the included studies is shown in *Table 4*.

Quality assessment

Of the nine studies identified, four were RCTs. Studies included small sample sizes at recruitment (range 30–65) and one study[48] did not report on the effectiveness of PhVIT but rather reported ARs only. Six studies used SC to assess the effectiveness of PhVIT and three studies[32,40,49]

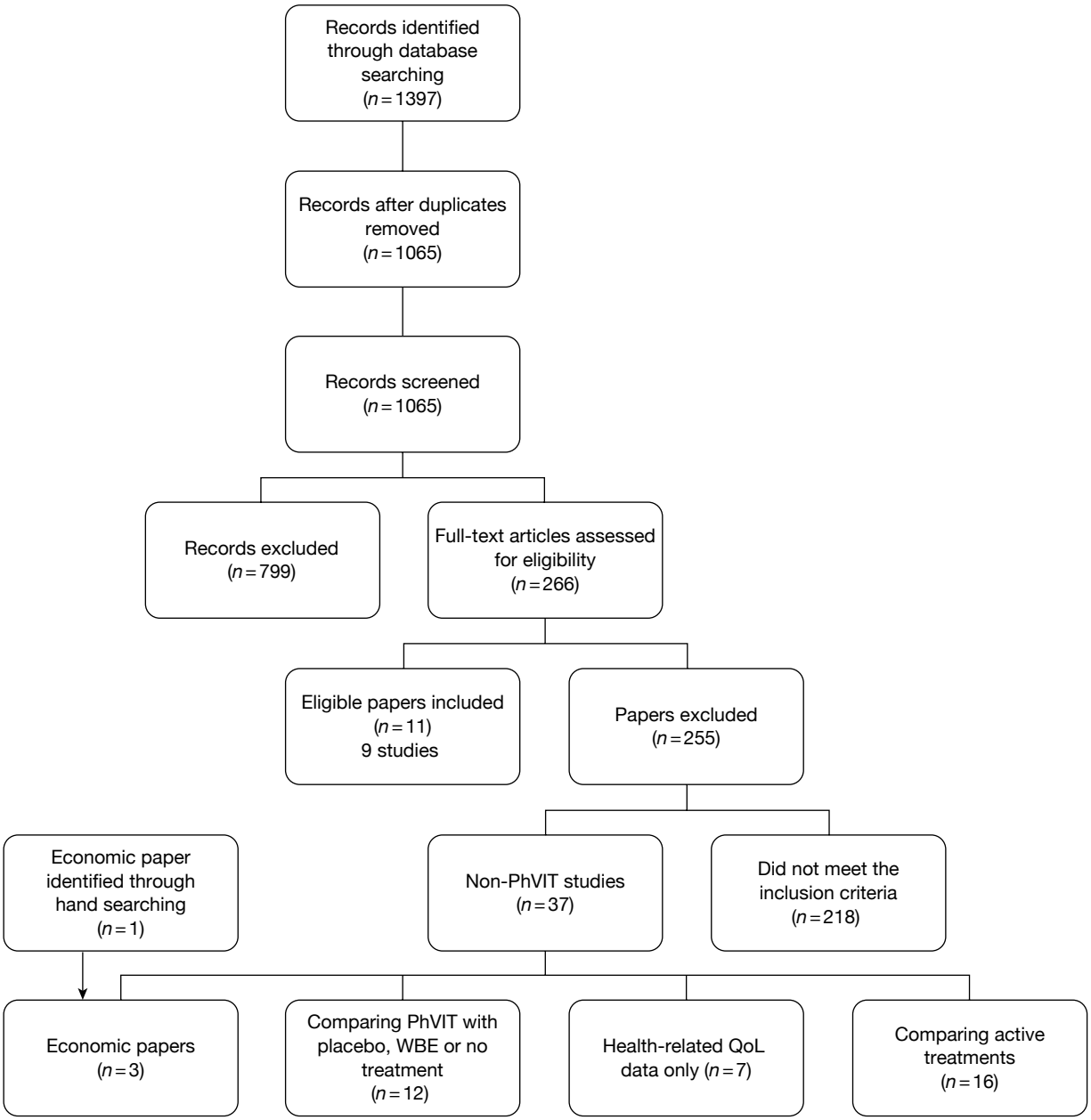

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

considered a subsequent FS, thereby further decreasing the final number of people assessed in these three studies.

The results of the quality assessment of included trials using CRD Report 4[34] are reported in *Appendix 4*. None of the RCTs[44,45,47,48] described the randomisation method used, so it was not possible to ascertain whether the method of allocation and its concealment were adequate.

Baseline comparability was achieved in eight studies. One study[45] reported the severity of reaction to initial sting across the groups but otherwise did not comment on the comparability of groups.

All studies reported their eligibility criteria and no co-interventions were identified. Only one[46] of the studies was blinded and, although the authors described it as a double-blind study, details of who was blinded were not reported.

All studies reported on the number of withdrawals but only one study[45] reported more than 20% dropout. Two studies[40,48] reported zero dropouts and one study[47] reported dropout for the experimental group but not for the historical control group. Where dropouts were reported there was imbalance in the rate of dropout between the arms for all but one study[49] and these imbalances were not explained or adjusted for. There was no evidence of more outcomes measured than reported.

Clinical effectiveness

Trial characteristics

The nine included studies compared PhVIT with an active treatment. Five compared PhVIT with a differing dose or protocol of PhVIT,[42–44,48,49] one compared PhVIT with a modified form of PhVIT[47] and three compared PhVIT with non-PhVIT.[32,40,45] Information on trial characteristics is presented in *Table 4*.

Four of the studies were RCTs,[44,45,47,48] two compared an intervention group with historical controls[42,43] and three were quasi-experimental with people allocated to groups by differing means.[32,40,49] Cadario *et al.*[40] alternated treatments in consecutive people, Patriarca *et al.*[32] offered sublingual PhVIT to those who had refused subcutaneous PhVIT, and Thurneer *et al.*[49] administered PhVIT in a rush protocol through the insect flying season and in a conventional protocol out of the insect flying season.

All but one study[48] reported the result of subsequent stings. Five of the studies[42–45,47] used a SC performed on all people to determine the effectiveness of treatment, thereby ensuring that outcome data were available for all people, and three studies reported the effects of accidental FSs.[32,40,49] Only three studies[32,40,47] reported on outcomes other than systemic reaction, that is, LLRs and local reactions (see *Table 4*). No studies reported on mortality although this is likely to be because there were no deaths rather than a failure of reporting. Data on ARs were available from all studies. Eight studies[32,40,42–45,47,49] reported details of systemic reaction to PhVIT and seven reported data on LLRs.[32,40,42,44,45,48,49] One study reported data on local reactions.[41]

Details of further trial characteristics are reported in *Table 5*. None of the studies was conducted in the UK and outcomes were measured at different time points between 4 days and > 3 years. Sponsorship was not reported in any studies, but four studies[40,45,47,48] were co-authored by the manufacturer and three[42–44] stated that the venom was provided by the manufacturer. Two studies[32,49] reported that the venom was provided by the manufacturer and the studies were co-authored by the manufacturer. No studies selected special populations although one[40] stated that people selected had to have 'significant risks of subsequent exposure whether in terms of actual physical risk of severe reactions or socially relevant impairment of the QoL due to fear of subsequent stings'; however, in their description of people included in the study they report on people with 'low risk'.

Inclusion/exclusion criteria

All studies recruited people who were shown to be allergic to Hymenoptera venom determined through skin tests and seven confirmed this diagnosis with IgE testing (the majority using RAST). No studies used a SC as a diagnostic tool or selected people on the duration of their allergy or particular demographics such as age or sex. Five studies[40,42–44,49] did not select people on species of venom allergy, two[32,45] selected wasp venom-allergic people only and two[47,48] included bee venom-allergic patients only. Severity of reaction was an inclusion criterion for

TABLE 4 Summary of included studies

Study ID	Intervention (no. of patients at end of study)	Comparator (no. of patients at end of study)	Design	Outcome data				ARs
				FS/SC	Systemic reaction	LLR	Other	
RCTs								
Golden 1980[41,44]	Pharmalgen: rush therapy (18)	Pharmalgen: step therapy (19) Pharmalgen: slow therapy (19)	RCT	FS/SC	Yes	No	No	Systemic reaction, LLR
Mosbech 1986[45]	Pharmalgen: aqueous induction and maintenance (3)	Alutard: depot induction and maintenance (7) Aquagen: aqueous induction and maintenance (9)	RCT	SC	Yes	No	No	Systemic reaction, LLR
Müller 1987[46,47]	Pharmalgen or Reless: HBV (14)	Modified Pharmalgen: monomethoxy polyethylene glycol-coupled HBV (17)	RCT	SC	Yes	Yes	No	Systemic reaction
Quercia 2001[48]	Pharmalgen: cluster (20)	Pharmalgen: rush (20) Depot cluster (15)	RCT	NA	No	No	No	Systemic reaction, LLR
Non-RCTs								
Cadario 2004[40]	Pharmalgen: aqueous induction and maintenance (18)	Alutard: depot induction and maintenance (27)	Quasi-experimental: interventions alternated in consecutive subjects	FS	Yes	No	local reaction	Systemic reaction, local reaction
Golden 1981[43]	Pharmalgen: 50 μg maintenance (19)	Pharmalgen: 100 μg maintenance[45] (18) In-house venom: 100 μg maintenance[28] (19)	Historical control group	SC	Yes	No	No	LLR
Golden 1981[42]	Pharmalgen: 6-weekly maintenance (29)	Pharmalgen: 4-weekly maintenance a (42) Pharmalgen: 4-weekly maintenance b (56)	Randomly selected patients from larger cohort compared with historical controls (some overlap of people)	SC	Yes	No	No	Systemic reaction, LLR
Patriarca 2008[32]	Pharmalgen: ultra-rush SCIT (20)	Aquagen: ultra-rush SLIT (17)	Case–control: people who declined SCIT were given SLIT	FS	Yes	Yes	No	Systemic reaction, LLR
Thurnheer 1983[49]	Pharmalgen: conventional Total for both arms (40)	Pharmalgen: rush	Quasi-experimental: groups determined by season	FS	Yes	No	No	Systemic reaction, LLR

HBV, honey bee venom; NA, not applicable; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 5 Trial characteristics

Study ID	Setting	Country	Design	Duration of trial	Sponsorship	Special population
RCTs						
Golden 1980[41,44]	NR	USA	RCT	20 weeks	Manufacturer provided venom	No
Mosbech 1986[45]	Two allergy clinics	Denmark	RCT	2.5–3 years	One author from Allergologisk Laboratorium A/S (producers of ALK Aquagen)	No
Müller 1987[46,47]	NR	Switzerland and South Africa	RCT	14 weeks	One author from ALK Abelló	No
Quercia 2001[48]	NR	Italy	RCT	4 days–6 weeks	One author from ALK Abelló	No
Non-RCTs						
Cadario 2004[40]	Eight medical care units, outpatient	Italy	Interventions alternated in consecutive subjects	≥ 3 years	One author from ALK Abelló	No[a]
Golden 1981[43]	NR	USA	Historical control group	20 weeks	Manufacturer provided venom	No
Golden 1981[42]	NR	USA	Randomly selected patients from larger cohort compared with historical controls (some overlap of people)	2.5–2.75 years	Manufacturer provided venom	No
Patriarca 2008[32]	Allergy department	Italy	People who declined SCIT were given SLIT	2 years	Manufacturer provided venom and one author from ALK Abelló	No
Thurnheer 1983[49]	Hospital with maintenance at family doctor	Switzerland	Quasi-experimental: groups determined by season	3 years	Manufacturer provided venom and one author from Pharmacia	No

NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

a Stated that people selected had to have 'significant risks of subsequent exposure whether in terms of actual physical risk of severe reactions or socially relevant impairment of the QoL due to fear of subsequent stings'. Patient table also includes people with low risk.

three studies.[40,48,49] Two studies[40,48] included only people with a grade 2 or higher reaction as determined by an adapted Mueller grading system.[50] One study[44] stated that people with sting-related anaphylaxis had been included. Only two studies reported any exclusion criteria, these being beta-blocker therapy, cardiovascular, renal or respiratory disease or pregnancy in one study[32] and no previous VIT in the other study[45] (*Table 6*).

Intervention characteristics

Details of the dosing protocols for each of the studies are described in *Table 7*. As many of the studies were looking at different regimens, the updosing protocols differed between the studies, with PhVIT given in between 6 and 35 doses over 3 hours to 16 weeks. The maintenance dosing protocols were more similar across the studies, with most studies reporting a maintenance dose of 100 µg every month/4 weeks. The exceptions to this were the studies by Golden *et al.*, one[43] of which compared a monthly 100-µg maintenance dose with a monthly maintenance dose of 50 µg and one[42] of which compared a 6-weekly 100-µg maintenance protocol with two historical groups who received a 100-µg maintenance dose every 4 weeks, and that by Müller *et al.*,[47] which compared a monthly maintenance dose of 200 µg with one of 100 µg. Outcomes were measured at between 2 weeks and 5 years of maintenance therapy. No trial reported pretreatment with a HDA; two studies stated that no pretreatment was used.

Patient characteristics

The number of people recruited to the studies ranged from 30 to 65, and the number included in the final analyses ranged from 19 to 56. The average age of participants was similar across studies and ranged from 35 to 49 years. All studies reported a higher percentage of males than females (between 57% and 88%). The severity of systemic reaction to the initial sting was reported in terms of Mueller grades[50] in four studies[32,40,48,49] and not at all by one study.[42] The remaining studies[43–45,47] reported severity by clinical symptoms (*Table 8*).

Outcomes

Although it was not their primary outcome, all but one study[48] reported clinical effectiveness outcomes; the study not reporting on clinical effectiveness reported only on ARs. The other eight studies reported the number of systemic reactions to re-stings and two reported the number of LLRs. For three studies[32,40,49] re-stings were FS and therefore not all people had been re-stung. The percentages of people re-stung in these studies were 24%,[40] 35%[32] and 60%.[49] The remaining studies used SC. The time point of any re-sting (FS or SC) varied between studies but all occurred during treatment.

The incidence of systemic reaction to re-sting ranged from 0.0%[40,44,45] to 36.4%[49] (*Table 9*). Two studies[42,43] compared the rate of systemic reaction across the arms of the study and neither reported a significant difference between the arms.

Large local reactions were reported in two studies (*Table 10*). The frequency of LLRs was similar in the two arms of the Müller study[47] (35.7% and 41.2%) and differed between PhVIT administered subcutaneously and PhVIT administered sublingually in the Patriarca study[32] (88.9% and 50.0% respectively).

Adverse reactions

Details of ARs during treatment were reported by eight studies: one study during induction only,[40] five during treatment (induction and maintenance)[32,44,47–49] and two during maintenance only.[42,45]

Systemic reactions during induction were reported in two studies. Cadario *et al.*[40] reported no difference in the frequency of systemic reactions in the aqueous and depot arms (11.1% and 7.4% respectively). Mosbech *et al.*[45] reported no systemic reactions in the PhVIT and non-PhVIT

TABLE 6 Inclusion and exclusion criteria

	Inclusion criteria							Exclusion criteria		
Study ID	Skin testing	IgE	Diagnostic SC	Severity of condition	Duration of condition	Demographics	Species	Other/recent treatments	Other illness	Other criteria
RCTs										
Golden 1980[41,44]	Intradermal	RAST	No	Sting-related anaphylaxis	No	No	Hymenoptera	No	No	No
Mosbech 1986[45]	Skin prick test	RAST	No	None	No	No	Yellow jacket (wasp)	No	No	No VIT previously
Müller 1987[46,47]	Intradermal	Yes	No	None	No	No	Honey bee	No	No	No
Quercia 2001[48]	Skin prick test and intracutaneous	RAST	No	≥ grade 2 Mueller[8]	NR	No	*Apis mellifera* (honey bee)	No	No	No
Non-RCTs										
Cadario 2004[40]	Skin prick test and intradermal	RAST	No	≥ grade 2 Mueller[8] (revised by Wuthrich)[51]	No	No	Hymenoptera	No	No	No
Golden 1981[43]	Intradermal	No	No	None	No	No	Hymenoptera	No	No	No
Golden 1981[42]	Intradermal	No	No	None	No	No	Hymenoptera	No	No	No
Patriarca 2008[32]	Skin prick test and intradermal	UniCAP® (Pharmacia)	No	None	No	No	*Vespula* (wasp)	Beta-blocker therapy	Cardiovascular, renal or respiratory disease	Pregnancy
Thurnheer 1983[49]	Intradermal	RAST	No	Grades 1–4 Mueller[50] with modifications by Huber[52]	No	No	Hymenoptera	No	No	No

UniCAP, an allergic immunoanalyser.

TABLE 7 Intervention characteristics

Study ID	Intervention	Updosing: frequency, dose(s) received on initial visit	Maintenance: dose and frequency	Duration of maintenance at time of reporting	Trade name/ supplier	Pretreatment
RCTs						
Golden 1980[41,44]	Slow therapy	**14 doses in 14 visits (weekly), total 14 weeks** Week 1: 0.01 µg	Week 17: 100 µg, week 20: 100 µg	6 weeks	Pharmalgen, Pharmacia	NR
	Step therapy	**10 doses in 8 visits, total 11 weeks** Initial: 1, 5, 10 µg (every 30 minutes)	Week 13: 100 µg, week 15: 100 µg, week 18: 100 µg	9 weeks	Pharmalgen, Pharmacia	NR
	Rush therapy	**6 doses in 4 visits (every 2 weeks), total 6 weeks** Initial: 1, 5, 10 µg (every 30 minutes)	100 µg every 4 weeks	14 weeks	Pharmalgen, Pharmacia	NR
Mosbech 1986[45]	Pharmalgen	**26 doses in 13 visits (twice weekly), total 13 weeks** (> one injection per visit initially until local swelling exceeded 5 cm in diameter) Initial: 0.2 ml of 0.001 µg/ml concentration	100 µg or the dose four times giving local swelling > 5 cm, 4 ± 1 weeks	2.5–3 years	Pharmalgen, Pharmacia	NR
	Alutard	**19 doses in 19 visits (weekly), total 19 weeks** Initial: 0.02 µg	100 µg or the dose four times giving local swelling > 8 cm, 6 ± 2 weeks	2.5–3 years	Alutard, ALK Abelló	NR
	Aquagen	**26 doses in 13 visits (twice weekly), total 13 weeks** (> one injection per visit initially until local swelling exceeded 5 cm in diameter) Initial: 0.2 ml of 0.001 µg/ml concentration	100 µg or the dose four times giving local swelling > 5 cm, 4 ± 1 weeks	2.5–3 years	Aquagen, ALK Abelló	NR
Müller 1987[46,47]	HBV	**9 doses in 7 visits (weekly), total 6 weeks** Week 0: 0.1, 1.0, 3.0 µg	100 µg weeks 7, 9, 12 and 16 then monthly	NR	Pharmalgen or Reless, Pharmacia	NR
	Monomethoxy polyethylene glycol-coupled HBV	**7 doses in 5 visits (weekly), total 4 weeks** Week 0: 0.5, 5.0, 10.0 µg	200 µg weeks 7, 8, 9 and 11 then monthly	NR	Pharmalgen, Pharmacia	NR
Quercia 2001[48]	Pharmalgen: cluster	**12 doses in 6 visits (every week), total 6 weeks** Week 1: five doses, 0.01, 0.1, 1.0, 3.0, 6.0 µg (hourly)	100 µg per visit weeks 2, 3 and 4 then every 4 weeks	5 years	Pharmalgen, ALK Abelló	No
	Pharmalgen: rush	**13 doses in 4 visits (every day), total 4 days** Day 1: four doses, 0.01, 0.1, 1.0, 2.0 µg (hourly)	100 µg per visit at weeks 2, 3 and 4 then every 4 weeks	5 years	Pharmalgen, ALK Abelló	No
	Depot cluster	**12 doses in 5 visits (weekly), total 5 weeks** Week 1: four doses, 0.03, 0.1, 0.3, 1.0 µg (hourly)	100 µg per visit at weeks 2, 3 and 4 then every 4 weeks	5 years	Alutard, ALK Abelló	No

Study ID	Intervention	Updosing: frequency, dose(s) received on initial visit	Maintenance: dose and frequency	Duration of maintenance at time of reporting	Trade name/ supplier	Pretreatment
Non-RCTs						
Cadario 2004[40]	Aqueous induction and aqueous maintenance	**12 doses in 8 visits (weekly), total 8 weeks** Week 1: 0.01, 0.1 µg (30 minutes between)	100 µg monthly	3 years	Pharmalgen, ALK Abelló	No
	Depot induction and depot maintenance	**15 doses in 15 visits (weekly), total 15 weeks** Week 1: 0.02 µg	100 µg monthly	3 years	Alutard, ALK Abelló	No
Golden 1981[43]	50 µg maintenance	**6 doses in 6 visits (weekly), total 6 weeks** Initial: 1 µg on first day	50 µg monthly	14 weeks	Pharmalgen, Pharmacia	NR
	100 µg maintenance[44]	**6 doses in 4 visits every 2 weeks, total 6 weeks**	100 µg monthly	14 weeks	Pharmalgen, Pharmacia	NR
	100 µg maintenance[28]	**12 doses in 9 visits, total 4 weeks**	100 µg monthly	2 weeks	In-house venom	NR
Golden 1981[42]	4-weekly maintenance a	NA	100 µg every 4 weeks	2 years	Pharmalgen, Pharmacia	NR
	6-weekly maintenance	NA	100 µg every 4 weeks for 2 years then 100 µg every 6 weeks	2 years + 25–36 weeks	Pharmalgen, Pharmacia	NR
	4-weekly maintenance b	NA	100 µg every 4 weeks	1 year	Pharmalgen, Pharmacia	NR
Patriarca 2008[32]	Ultra-rush SCIT	**6 doses in 1 visit (every 30 minutes), total 3 hours** Day 1: 0.1 µg	100 µg monthly	2 years	Pharmalgen, ALK Abelló	NR
	Ultra-rush SLIT	**10 doses in 1 visit (every 20 minutes), total 3 hours** Initial dose dilution: 1 :10,000, one drop	10 drops of pure extract given three times a week	2 years	Aquagen, ALK Abelló	NR
Thurnheer 1983[49]	Conventional	**24 doses in 10 visits (weekly), total 10 weeks** Day 1: 0.1 ml (0.0001 µg/ml), 0.1 ml (0.001 µg/ml), 0.1 ml (0.01 µg/ml),	1.0 ml twice a week for 4 weeks, 1.0 ml weekly for 4 weeks, 1.0 ml every 2 weeks for 8 weeks, 1.0 ml monthly	3 years	Pharmalgen, ALK Abelló	NR
	Rush	**35 doses in 10 visits (daily), total 10 days** Day 1: 0.1, 0.2, 0.4, 0.8 ml (0.0001 µg/ml)	1.0 ml twice a week for 4 weeks, 1.0 ml weekly for 4 weeks, 1.0 ml every 2 weeks for 8 weeks, 1.0 ml monthly	3 years	Pharmalgen, ALK Abelló	NR

HBV, honey bee venom; N/A, not available; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 8 Patient characteristics

Study ID	Name of intervention	*n*	Age (range), years	Male, *n* (%)	Severity, *n* (%)	Loss to follow-up			
						Reason	Total *n* (%)	Final *n*	ITT
RCTs									
Golden 1980[41,44]	Slow therapy	22	NR	NR	Cutaneous signs only: 7/64 (10.9) Urticaria: 44/64 (68.8) Dizziness or hypotension: 43/64 (67.2) Throat swelling or hoarseness: 32/64 (50.0) Dyspnoea: 31/64 (48.4) Loss of consciousness: 19/64 (29.7) Wheezing: 5/64 (7.8)	2 no SC: not reached maintenance due to systemic reaction and local reaction to VIT 1 no SC: not reached maintenance as 2-month interruption in therapy	3 (13.6)	19	No
	Step therapy	20				1 no SC because of cardiac status	1 (5.0)	19	No
	Rush therapy	22				2 no SC because of illness or cardiac status 1 no SC: only treated with *Polistes* wasp venom 1 no SC: anti-venom IgE was in doubt at the time	4 (18.2)	18	No
Mosbech 1986[45]	Pharmalgen	10	46 (21–62)	NR	Urticaria/angioedema: 8/10 (80%) Respiratory symptoms: 6/10 (60%) CNS symptoms: 5/10 (50%)	1 immunotherapy with bee venom 1 local and systemic side effects 1 other disease 1 lack of time 3 no SC: reason unclear	7 (70.0)	3	No
	Alutard	12	41 (29–79)	NR	Urticaria/angioedema: 11/12 (91.7%) Respiratory symptoms: 7/12 (58.3%) CNS symptoms: 9/12 (75%)	1 psychic reactions 1 other disease 1 unknown 1 emigration 1 no SC: reason unclear	5 (41.7)	7	No
	Aquagen	10	40 (24–60)	NR	Urticaria/angioedema: 7/10 (70) Respiratory symptoms: 3/10 (30) CNS symptoms: 7/10 (70)	1 no SC: reason unclear	1 (10.0)	9	No
Müller 1987[46,47]	HBV	17	34.5 (17–57)	15 (88.2)	Urticaria/angioedema: 3/17 (17.6) Respiratory: 10/17 (58.8) Shock: 4/17 (23.5)	2 side effects 1 went abroad	3 (17.6)	14	No
	Monomethoxy polyethylene glycol-coupled HBV	17	34.6 (17–70)	13 (76.5)	Urticaria/angioedema: 5/17 (29.4) Respiratory: 9/17 (52.9) Shock: 3/17 (17.6)	None	0 (0)	17	No

Study ID	Name of intervention	*n*	Age (range), years	Male, *n* (%)	Severity, *n* (%)	Loss to follow-up			
						Reason	Total *n* (%)	Final *n*	ITT
Quercia 2001[48]	Pharmalgen: cluster	20	46.35 (28–76)	16/20 (80)	Grade 1: 0 (0.0) Grade 2: 10 (50.0) Grade 3: 5 (25.0) Grade 4: 5 (25.0)	NA	0 (0)	20	NA
	Pharmalgen: rush	20	48.5 (18–73)	16/20 (80)	Grade 1: 1 (5.0) Grade 2: 5 (25.0) Grade 3: 11 (55.0) Grade 4: 3 (15.0)	NA	0 (0.0)	20	NA
	Depot cluster	15	41.47 (18–68)	13/15 (86.7)	Grade 1: 1 (7.7) Grade 2: 4 (30.8) Grade 3: 6 (46.2) Grade 4: 4 (30.8)	NA	0 (0.0)	15	NA
Non-RCTs									
Cadario 2004[40]	Aqueous induction and aqueous maintenance	18	42.6 (19–69)	15 (83.3)	Grade 2: 9 (50.0) Grade 3: 0 (0.0) Grade 4: 9 (50.0)	NA	0 (0.0)	18	NA
	Depot induction and depot maintenance	27	39.0 (15–68)	19 (70.4)	Grade 2: 5 (18.5) Grade 3: 9 (33.3) Grade 4: 13 (48.1)	NA	0 (0.0)	27	NA
Golden 1981[43]	50 µg maintenance	23	NR	14 (60.9)	Cutaneous signs only: 10/65 (15.4) Urticaria: 50/65 (77) Dizziness or hypotension: 41/65 (63.1) Throat swelling or hoarseness: 26/65 (40) Dyspnoea/wheezing: 27/65 (41.5) Loss of consciousness: 22/65 (33.8)	4 not available for SC	4 (17.4)	19	No
	100 µg maintenance[44]	22		13 (59.1)		2 no SC: illness or cardiac status 1 no SC: only treated with *Polistes* wasp venom 1 no SC: anti-venom IgG was in doubt at the time	4 (18.2)	18	No
	100 µg maintenance[28]	20		13 (65.0)		1 no SC: could not tolerate maintenance dose	1 (5.0)	19	No

continued

TABLE 8 Patient characteristics (*continued*)

Study ID	Name of intervention	*n*	Age (range), years	Male, *n* (%)	Severity, *n* (%)	Loss to follow-up			
						Reason	Total *n* (%)	Final *n*	ITT
Golden 1981[42]	4-weekly maintenance a	NR	NR	NR	NR	1 not available for SC None others stated	NR	42	No
	6-weekly maintenance	30	NR	NR	NR	1 not available for SC	1 (3.3)	29	No
	4-weekly maintenance b	NR	NR	NR	NR	1 not available for SC None others stated	NR	56	No
Patriarca 2008[32]	Ultra-rush SCIT	20	35 (±14)	16/20 (80)	Grade 1: 1 (5) Grade 2: 9 (45) Grade 3: 4 (20) Grade 4: 6 (30)	NA	0 (0.0)	20	No
	Ultra-rush SLIT	21	38 (±16)	15/21 (71.4)	Grade 1: 3 (14.3) Grade 2: 11 (52.4) Grade 3: 3 (14.3) Grade 4: 4 (19.0)	2 lack of compliance 2 continued but did not have other outcomes measured	4 (19.0)	17	No
Thurnheer 1983[49]	Conventional	21	36.3 (±15.4) (6–69)	12/21 (57.1)	Grade 1: 2 (9.5) Grade 2: 3 (14.3) Grade 3: 11 (52.4) Grade 4: 5 (23.8)	1 pregnancy 1 treatment failure	2/42 (4.8)	40	No
	Rush	21	36.1 (±19.3) (11–70)	13/21 (61.9)	Grade 1: 1 (4.8) Grade 2: 5 (23.8) Grade 3: 9 (42.9) Grade 4: 6 (28.6)	NA			

CNS, central nervous system; HBV, honey bee venom; NA, not applicable; NR, Not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

TABLE 9 Number of people re-stung and the number of systemic reactions reported

Study ID[a]	Name of intervention	FS or SC (*n*)	Time point	Final *n*	Re-stung, *n* (%)	Systemic reaction, *n* (%)	*p*-value[b]
RCTs							
Golden 1980[41,44]	Slow therapy	FS (4), SC (52)	18–20 weeks of VIT	19	19 (100)	0 (0.0)	NR
	Step therapy			19	19 (100)		
	Rush therapy			18	18 (100)		
Mosbech 1986[45]	Pharmalgen	SC	2.5–3 years	3	3 (100)	0 (0.0)	NR
	Alutard			7	7 (100)	0 (0.0)	
	Aquagen			9	9 (100)	0 (0.0)	
Müller 1987[46,47]	HBV	SC	~14 weeks	14	14 (100)	2 (14.3) (angioedema)	NR
	Monomethoxy polyethylene glycol-coupled HBV	SC	~14 weeks	17	17 (100)	4 (23.5) [urticaria: 1 (5.9), respiratory: 3 (17.6), shock: 2 (11.8), gastrointestinal: 2 (11.8)]	
Non-RCTs							
Cadario 2004[40]	Aqueous induction and aqueous maintenance	FS	3 years	18	5 (27.8)	0 (0.0)	NR
	Depot induction and depot maintenance	FS	3 years	27	6 (22.2)	0 (0.0)	
Golden 1981[43]	50 µg maintenance	SC	20 weeks of VIT	19	19 (100)	4 (21.1)	0.0587
	100 µg maintenance[44]	SC	20 weeks of VIT	18	18 (100)	0 (0.0)	
	100 µg maintenance[28]	SC	6 weeks of VIT	19	19 (100)	NR	NR
Golden 1981[42]	4-weekly maintenance a	SC	2 years	42	42 (100)	1 (2.4)	>0.05
	6-weekly maintenance	SC	2 years + 6–9 months	29	29 (100)	1 (3.4)	
	4-weekly maintenance b	SC	1 year	56	56 (100)	1 (1.8)	
Patriarca 2008[32]	Ultra-rush SCIT	FS	During treatment	20	9 (45)	1 (11.1) (dizziness)	NR
	Ultra-rush SLIT	FS	During treatment	17	4 (23.5)	1 (25.0) [2/6 (33.3%) stings at 12 and 24 months (throat constriction)]	
Thurnheer 1983[49]	Conventional	FS (22), SC (2)	NR	40	24 (60)[c]	4 (36.4)[c] [3 (27.3) patients diminished systemic reaction (mild symptoms), 1 (9.1) patient same systemic reaction)	NR
	Rush		NR			3 (27.3)[c] [diminished systemic reaction (mild symptoms)]	NR

HBV, honey bee venom; NR, Not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

a Quercia *et al.*[48] does not report any outcome data.

b Difference between arms in rates of systemic reaction.

c 24/40 patients were re-stung; 11 people in each arm were able to identify the insect and systemic reaction rates are reported for them

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TABLE 10 Number of people re-stung and the number of LLRs reported

Study ID	Name of intervention	SC or FS	Time point	Final *n*	Re-stung, *n* (%)	LRR, *n* (%)
Müller 1987[46,47]	HBV	SC	~14 weeks	14	14 (100)	5 (35.7)
	Monomethoxy polyethylene glycol-coupled HBV	SC	~14 weeks	17	17 (100)	7 (41.2)
Patriarca 2008[32]	Ultra-rush SCIT	FS	During treatment	20	9 (45.0)	8 (88.9)
	Ultra-rush SLIT	FS	During treatment	17	4 (23.5)	2 (50.0) [2/6 (33.3%) stings at 1 and 12 months]

HBV, honey bee venom; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
Data are for number of people unless otherwise stated.

(Aquagen) arms; however, 3/10 people in the non-PhVIT (Alutard) arm experienced systemic reactions during the induction phase. Five studies[32,44,47–49] reporting the frequency of systemic reactions during the whole treatment period reported frequencies of between 0.0% and 38.1%. The statistical difference between arms was calculated in two of these studies[32,44] and no statistically significant difference was found. A third study reported the same rates in each arm (*Table 11*).[49]

Two studies[42,45] reported the rates of systemic reactions during maintenance therapy. In one,[42] no reactions were reported, and in the other[45] 3/10 people experienced a systemic reaction (see *Table 11*).

Cadario *et al.*[40] reported general local reactions during induction and found a significantly higher rate of local reactions in the aqueous treatment arm [7/18 (38.9%) patients, 13/216 (6.0%) doses] than in the depot arm [4/27 (14.8%) patients, 5/405 (1.2%) doses] [$p = 0.0328$ (patients), $p = 0.0004$ (doses)] (*Table 12*).

The four studies[32,44,48,49] reporting LLRs during treatment reported frequencies of LLR from subcutaneous PhVIT of between 6.7% and 60.0%. People receiving sublingual PhVIT[32] reported no LLRs. The difference in LLRs between arms was reported in one study;[41,44] no difference in rates between the arms was observed. Of the two studies[42,45] reporting LLRs during the maintenance phase of treatment, one[42] reported LLRs on average of 6 per 100 injections for the 4-weekly maintenance programme and 2 per 100 injections for the 6-weekly maintenance programme. The second study[45] reported that no LLRs occurred in any of the treatment arms (see *Table 12*).

Indirect analysis and mixed-treatment comparisons

The possibility of conducting a MTC was investigated when no head-to-head studies were identified that compared PhVIT and alternative treatment options available in the NHS without VIT such as advice on the avoidance of bee and wasp venom, HDA and AAI prescription and training. It was planned that studies that investigated non-VIT against non-PhVIT would be used in the MTC analysis to estimate the indirect treatment effect for PhVIT versus non-VIT; however, given the small number of trials and lack of head-to-head comparisons of PhVIT versus any intervention, pooling of all outcomes using standard meta-analysis was not possible. Any indirect analysis comparing PhVIT with any other intervention (including different doses and administration protocols of PhVIT) would be inappropriate because of sparse data and heterogeneity in the study designs and the characteristics of non-PhVIT and non-VIT interventions.

TABLE 11 Systemic reactions

Study ID	Name of intervention	Definition	Timing	*n* (%)	*p*-value
RCTs					
Golden 1980[41,44]	Slow therapy	Systemic reaction	During VIT	4/22 (18.2) patients, 7/450 (1.6) doses	> 0.05
	Step therapy			2/20 (10.0) patients, 4/260 (1.5) doses	
	Rush therapy			4/22 (18.2) patients, 4/233 (1.7) doses	
Mosbech 1986[45]	Pharmalgen	Systemic reaction	Updosing and maintenance	0/10 (0.0) patients, 0/3 (0.0) patients	NR
	Alutard			3/10 (33.3) patients, 0/7 (0.0) patients	
	Aquagen			0/12 (0.0) patients, 0/9 (0.0) patients	
Müller 1987[46,47]	HBV	Objective systemic reaction	During VIT	4/14 patients (28.6)	NR
	Monomethoxy polyethylene glycol-coupled HBV			2/17 patients (11.8)	
Non-RCTs					
Cadario 2004[40]	Aqueous induction and aqueous maintenance	During induction systemic reaction[b,c]	Early = within 60 minutes	All: 2/18 (11.1) patients, 9/216 (4.1) doses; early: 2/18 (11.1) patients, 9/216 (4.1) doses; late: 0/18 (0.0) patients, 0/216 (0) doses	All: 0.3205 (patients), 0.0339 (doses)
		Clinician reported using criteria of Lockey *et al.*[53] and Mueller[50]	Late = after 60 minutes		
	Depot induction and depot maintenance			All: 2/27 (7.4) patients, 7/405 (1.7) doses; early: 0 (0.0) patients, 0 (0.0) doses; late: 2/27 (7.4) patients, 7/405 (1.7) doses	
Golden 1981[42]	4-weekly maintenance a	Systemic reaction	During maintenance	NR	NR
	6-weekly maintenance			0/30 (0.0)	
	4-weekly maintenance b		NR	NR	
Patriarca 2008[32]	Ultra-rush SCIT	Mild general side effects (dysphagia, itching, headache and stomach ache	During VIT	1/20 (5) patients	> 0.05
	Ultra-rush SLIT			2/21 (9.5) patients	
Quercia 2001[48]	Pharmalgen: cluster	Systemic reaction	During VIT	1/20 (5.0) patients	Unclear
	Pharmalgen: rush	Grades 1–4 Mueller		7/20 (35.0) patients	
	Depot cluster			0/15 (0.0) patients	
Thurnheer 1983[49]	Conventional	All systemic reaction grades	During 3-year treatment	All: 8/21 (38.1) patients; grades 1–2: 7/21 (33.3) patients; grades 3–4: 1/21 (4.8) patients	NR
	Rush	Systemic reaction grades 1–2		All: 8/21 (38.1) patients; grades 1–2: 5/21 (23.8) patients; grades 3–4: 3/21 (14.3) patients	
		Systemic reaction grades 3–4			

HBV, honey bee venom; NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
a Golden *et al.*[43] did not report on ARs.
b Systemic reactions were all grade 2 and local reactions were oedema/erythema apart from one late local reaction, which was local pruritus.
c One patient also reported a mild systemic reaction during the maintenance phase.

Additional data

Because of the lack of relevant comparative data on PhVIT, observational non-comparative studies of PhVIT have also been considered as well as comparative studies of non-PhVIT.

Observational studies of Pharmalgen

In addition to the comparative studies of PhVIT included in this review the searches identified 17 observational studies of PhVIT in the treatment of bee and wasp venom allergy (*Table 13*).

TABLE 12 Local reactions

Study ID[a]	Name of intervention	Definition	Timing	*n* (%)	*p*-value
RCTs					
Golden 1980[41,44]	Slow therapy	LLR	During VIT	9/22 (40.9) patients, 37/450 (8.2) doses	
	Step therapy			12/20 (60.0) patients, 31/260 (11.9) doses	
	Rush therapy			11/22 (50.0) patients, 22/233 (9.4) doses	
Mosbech 1986[45]	Pharmalgen	LLR	During maintenance	1/10 (10.0) patients	NR
	Alutard			0/12 (0.0) patients	
	Aquagen			0/10 (0.0) patients	
Non-RCTs					
Cadario 2004[40]	Aqueous induction and aqueous maintenance	During induction local reaction[b] Clinician reported using criteria of Lockey *et al.*[53] and Mueller[50]	Early = reactions within 60 minutes Late = reactions after 60 minutes	All: 7/18 (38.9) patients, 13/216 (6.0) doses; early: 1/18 (5.6) patients, 1/216 (0.5) doses; late: 6/18 (33.3) patients, 12/216 (5.6) doses	All: 0.0328 (patients), 0.0004 (doses)
	Depot induction and depot maintenance			All: 4/27 (14.8) patients, 5/405 (1.2) doses; early: 1/27 (3.7) patients, 1/405 (0.2) doses; late: 3/27 (11.1) patients, 4/405 (1.0) doses	
Golden 1981[42]	4-weekly maintenance a	LLR	During maintenance	6 per 100 injections	> 0.05
	6-weekly maintenance	LLR		2 per 100 injections	
	4-weekly maintenance b	LLR	NR	NR	
Patriarca 2008[32]	Ultra-rush SCIT	LLR	During VIT	3/20 (15) patients	NR
	Ultra-rush SLIT			0/21 (0.0)	
Quercia 2001[48]	Pharmalgen: cluster	LLR (erythema > 10 cm)	During VIT	4/20 (20.0) patients	Unclear
	Pharmalgen: rush			4/20 (20.0) patients	
	Depot cluster			1/15 (6.7) patients	
Thurnheer 1983[49]	Conventional	LLR	During 3-year treatment	5/21 (23.8) patients	NR
	Rush			3/21 (14.3) patients	

NR, not reported; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.
a Golden *et al.*[43] did not report on ARs.
b Müller *et al.*[46,47] did not report on LLR as ARs.

It is likely that some of these papers are multiple publications from the same studies but in the following description they are assumed to be independent. All 17 studies assessed the rate of systemic reactions to subsequent stings, either FS or SC, after or during PhVIT.

All but one study[54] was conducted in Europe and all studies used a maintenance dose of 100 µg/ml Pharmalgen. The number of people receiving treatment ranged from 10 to 562 and the number of re-stings reported in each study ranged from 3 to 290. Three studies[55–57] included only children. Five studies[58–62] split results by insect venom type and a further two[63,64] reported outcomes only for individuals with a bee venom allergy.

The timing of the sting differed between studies and as such has an important bearing on the rates of systemic reaction reported. Four[54,60,64,65] reported re-sting during maintenance, four[59,62,63,66]

during updosing and maintenance, five[57,61,67–69] after PhVIT, two[55,70] during or after PhVIT and two[56,58] during and after PhVIT.

The reported rates of systemic reaction ranged between 0.0% and 32.7%. This large range reflects differences in the timing of re-stings, with 12 studies reporting data on re-stings before the completion of PhVIT. For the studies reporting systemic reactions after PhVIT, three smaller studies[67–69] reported no systemic reactions, two larger studies reported 4/200 (2.0%)[56] and 8/274 (2.9%)[58] systemic reactions, and the remaining two studies reported 1/29 (3.4%)[57] and 25/200 (12.5%)[61] systemic reactions.

Comparative studies of venom immunotherapy other than Pharmalgen

Although the remit of this review was to assess the clinical effectiveness and cost-effectiveness of PhVIT for the treatment of bee and wasp venom allergy, as discussed in *Chapter 1, Venom immunotherapy*, there are other VIT products that are available to treat bee and wasp venom allergy. The searches for this review identified one meta-analysis[71] and two systematic reviews[33,72] reporting on comparative studies of non-PhVIT products in the population of interest, and an overview of the publications is given in *Table 14*.

The AG assessed the systematic reviews[33,72] for quality using the Database of Abstracts of Reviews of Effects (DARE) quality assessment tool.[88] Both were shown to be of high quality (*Table 15*). One of the high-quality reviews was a Cochrane review that is ongoing, and the AG have worked in collaboration with this group on a number of systematic reviews.

Both of the systematic reviews[33,72] and the meta-analysis[71] conclude that VIT is effective in preventing future systemic reactions to venom in venom-allergic people.

Health-related quality of life

Although some studies have assessed the clinical efficacy of VIT, less research has been conducted on the psychological effects of VIT and Hymenoptera venom allergy. Frequency of re-sting in individuals who have undergone VIT is varied, and some individuals may not be stung again post VIT. However, these individuals may experience anxiety related to the possibility of a future sting, which may impact on their QoL. QoL has been assessed in a series of papers by Oude Elberink,[82–84,87] and a tool has been developed to specifically measure this: the Vespid Allergy Quality of Life Questionnaire (VQLQ).[84] The VQLQ has been found to have adequate cross-sectional and longitudinal validity.[89]

None of the included studies in our review reported data on the anxiety levels or the QoL of people receiving PhVIT. However, in the wider literature there have been several papers published looking at the effect of VIT on people's anxiety levels and their QoL. The current Cochrane review of VIT for the prevention of allergic reactions to insect stings[33] is investigating the evidence related to the QoL of VIT.

The Cochrane group searches identified four publications of RCTs reporting QoL data (*Table 16*). The relationship between the different publications (Oude Elberink *et al.*[82–84,87]) is not clear and it is possible that one publication reports data on people who are also included in another publication. Therefore, for the purpose of this review it is assumed that the publications of Oude Elberink relate to two separate RCTs, one RCT of VIT for the treatment of adults with a history of anaphylactic reaction to yellow jacket sting (Oude Elberink *et al.*[82–84]) and one RCT of VIT for the treatment of adults with a history of cutaneous reaction to yellow jacket sting (Oude Elberink *et al.*[87]).

TABLE 13 Characteristics of non-comparative Pharmalgen VIT studies

Study ID	Country	Maintenance dose	*n*	No. of re-stings	No. of systemic reactions[a]	Timing of stings	Type of sting	Comments	Special population
Carballada 2003[70]	Spain	100 µg/ml	241	84	12	During or after treatment	FS	84 stings in 58 patients	
Carballada 2009[55]	Spain	100 µg/ml	21	7 patients	0	During maintenance or after	FS		4–16 years old
Carballada 2010[58]	Spain	100 µg/ml	Bee 438, wasp 124	Bee 130, wasp 68 Bee 62, wasp 14	Bee 5, wasp 0 Bee 3, wasp 0	During treatment After treatment	FS	6 patients had a maintenance dose of 200 µg/ml and 7 people could not tolerate Pharmalgen and were changed to Aquagen Do not distinguish between people or re-stings	
Fricker 1997[66]	Switzerland	100 µg/ml	10	9	1	During treatment	3 FS, 6 SC	9 stings in 6 patients	Confirmed urticaria pigmentosa
Graft 1987[56]	USA	100 µg/ml	66	200 68	4 0	During or after treatment After at least 2 years of treatment	130 FS, 70 SC	200 stings in 49 children	4–17 years old
Haeberli 2003[59]	Switzerland	100 µg/ml	Bee 158, wasp 101	161; bee 104 (21 early), wasp 57	41; bee 34, wasp 7	During treatment	SC	21 bee venom-allergic patients had an SC within 6 months of treatment	Some patients heavily exposed to bees/wasps
Haugaard 1991[67]	Denmark	100 µg/ml	25	28	0	After treatment (mean 25.2 months, range 12–36 months)	SC	2 patients could tolerate only 60 µg/ml, and 1 only 20 µg/ml	
Kalogeromitros 2010[65]	Greece	100 µg/ml	49	59	1	During maintenance	FS	59 stings in 14 patients	
Kochuyt 1994[60]	Belgium	100 µg/ml	217	290; bee 213, wasp 77	1; bee 1, wasp 0	During 12-week maintenance (19 months' treatment + bees mean 25 months (range 5–76) wasps mean 31.5 months (range 3–96)	FS	290 stings in 65 patients; bees 213 stings in 17 patients, wasps 77 stings in 48 patients	

Study ID	Country	Maintenance dose	*n*	No. of re-stings	No. of systemic reactions[a]	Timing of stings	Type of sting	Comments	Special population
Lerch 1998[61]	Switzerland	100 µg/ml	358	200; bee 120, wasp 80	25; bee 19, wasp 6	After ≥ 3 years of treatment stopped	FS		
Müller 1989[63]	Switzerland	100 µg/ml	67	67 (29 early, 38 late)	15 (7 early)	During treatment	SC	18 patients had a 200 µg/ml maintenance dose; 29 patients had an SC in the first year of VIT (mean 4.41 ± 2.29 months), the remainder had an SC later in VIT treatment (mean 60.6 ± 21.3 months)	All bee allergic
Müller 1992[62]	Switzerland	100 µg/ml	Bee 148, wasp 57	Bee 148 (36 early), wasp 57	Bee 34 (6 early), wasp 5	During treatment	SC	31 patients had a maintenance dose of 200 µg/ml; 36 beekeepers had an SC early into maintenance and the rest after at least 3 years of VIT	
Ramirez 1981[54]	USA	100 µg/ml	22	12 patients	1 patient	During maintenance	SC	Itchy eyes and ears 20 minutes after sting	
Sanchez-Machin 2010[64]	Spain	100 µg/ml	54	3 patients	0	During maintenance	FS		All bee allergic
Schiavino 2004[68]	Italy	100 µg/ml	57	23 patients	0	After treatment	FS		
Szymanski 1995[69]	Poland	100 µg/ml	21	9 patients	0	After treatment	SC	12 patients did not have SC because of contraindications or lack of consent	
Urbanek 1985[57]	Germany	100 µg/ml	66	29 patients	1 patient	1 year after treatment	SC	2 years after treatment 2/14 mild systemic reaction	4–20 years old

Treatment, updosing and maintenance phase; early, sting performed within 12 months of starting VIT; late, sting performed ≥ 12 months after starting VIT.
a Number of re-stings unless stated otherwise.

TABLE 14 Summary of previous/ongoing systematic reviews/meta-analyses

	Ross[71]	Watanabe[72]	Elremeli[33]
Publication year	**2000**	**2010**	**In press**
Databases searched (dates)	MEDLINE (1966–96)	MEDLINE; LILACS; EMBASE; SciSearch; SciELO; Cochrane Database of Systemic Reviews (all searched from beginning to 2008)	CENTRAL (2010 issue 4–); MEDLINE (2005–10); EMBASE (2007–10); PsycINFO (1806–2010); AMED (1985–2010); LILACS (1982–2010); SIGLE EAACI (2008–10), AAAAI (2008–11) Plus details of ongoing trials were searched using the *m*RCT; the World Health Organization International Clinical Trials Registry platform; the Australian and New Zealand Clinical Trials Registry; the US National Institutes of Health Ongoing Trials Register; the Ongoing Skin Trials Register
No. of included studies	8	4	8
References of included studies	Graft 1984,[73] Hunt 1978,[28] Müller 1979,[74] Schuberth 1983,[75] Thurneer 1983,[49] Tsicopoulos 1988,[76] Wyss 1993,[77] Yunginger 1979[78]	[a]Brown 2003,[79] Hunt 1978,[28] Schuberth 1983,[75] Valentine 1990[80]	[a]Brown 2003,[79] Golden 2009,[81] Hunt 1978,[28] Oude Elberink 2001[82]/Oude Elberink 2002[83]/[b]Oude Elberink 2006,[84] Oude Elberink 2009,[85] Schuberth 1983,[75] Severino 2008,[86] Valentine 1990[80]
Design of included studies	Seven of the eight were open trials and all were 'comparisons of the people's history with post-treatment experience'	RCTs comparing Hymenoptera VIT with placebo or emergency treatment	RCTs comparing VIT with placebo, no treatment or back-up treatment for prevention of fatal insect sting anaphylaxis such as education and provision of self-administered adrenaline were included
Other inclusion criteria	Full papers in English in refereed journals. Studies of subcutaneous VIT	None	All participants with a previous systemic reaction or LLR to any insect sting and a positive skin test and/or serum-specific IgE to insect venom were included in this review, regardless of age, gender, ethnicity or duration of insect sting allergy Studies using standardised venom extract in any form of immunotherapy (subcutaneous or sublingual) were included. All appropriate allergens were included at all doses and all durations of treatment. It was also planned to include studies that used a mix of different extracts, e.g. bee and wasp together Placebo, no treatment or back-up treatment for prevention of fatal insect sting anaphylaxis such as education and provision of self-administered adrenaline were included. In RCTs comparing more than one treatment arm to control group, only the treatment arm using standard venom extract compared with a control group was included in the analysis

TABLE 14 Summary of previous/ongoing systematic reviews/meta-analyses (*continued*)

	Ross[71]	Watanabe[72]	Elremeli[33]
Publication year	**2000**	**2010**	**In press**
Exclusion criteria	Studies of oral, sublingual or other routes of administration	Other routes of administration such as sublingual or oral were excluded	No other exclusion criteria
Reported outcomes	Protection against a major systemic reaction, specific IgE, IgG tiers, ARs	Changes in clinical manifestation after SC or accidental stings, indication for VIT, changes in levels of venom-specific IgE or IgG antibodies	Systemic reaction to FS or SC, local reaction to FS or SC, QoL, ARs
Conclusions	The findings of this meta-analysis support the conclusion that specific immunotherapy is effective in the treatment of Hymenoptera venom hypersensitivity	Specific immunotherapy should be recommended for adults and children with moderate to severe reactions, but there is no need to prescribe it for children with skin reactions alone, especially if the exposure is very sporadic. On the other hand, the risk–benefit relation should always be assessed in each case	Review in progress

AMED, Allied and Complementary Medicine Database; CENTRAL, Cochrane Central Register of Controlled Trials; LILACS, Latin American and Caribbean Health Sciences Literature; *m*RCT, metaRegister of Controlled Trials; SciELO, Scientific Electronic Library Online; SIGLE, System for Information on Grey Literature in Europe.

a Brown 2003 studies the effectiveness in fire ants, which do not occur in the UK and are not treated with Pharmalgen.

b For the purpose of this review it is assumed that the publications of Oude Elberink relate to two separate RCTs: one RCT of VIT for the treatment of adults with a history of anaphylactic reaction to yellow jacket sting (Oude Elberink *et al.*[82–84]) and one RCT of VIT for the treatment of adults with a history of cutaneous reaction to yellow jacket sting (Oude Elberink *et al.*[87]).

TABLE 15 Quality assessment of systematic reviews of non-Pharmalgen VIT studies

	Watanabe[72]	Cochrane[33]
Are inclusion/exclusion criteria reported that address the review questions?	Good	Good
Is there evidence of a substantial effort to search for all relevant research literature?	Good	Good
Is the validity of included studies adequately assessed?	Good	Good
Is sufficient detail of the individual studies presented?	Good	Good
Are the primary studies summarised appropriately?	Good	Good

Both trials randomised consenting people to either VIT or an EpiPen. At the end of the treatment period those who had been randomised to an EpiPen were given the opportunity to receive VIT. People were asked to complete the VQLQ, the State-Trait Anxiety Inventory (STAI) and a burden of treatment (BOT) question [people were asked to weigh the advantages and disadvantages of their treatment on a 7-point scale, ranging from extremely positive (score 1) to extremely negative (score 7)]. All measures were taken before treatment and after 1 year of treatment. Oude Elberink *et al.*[84] also reported results of accidental re-stings after 1 year of treatment.

Additional information

Vespid Allergy Quality of Life questionnaire

In a study of 29 people with a history of LLR to yellow jacket sting, Oude Elberink *et al.*[87] reported that 53% had a significant improvement in QoL score (an increase of at least 0.5 points in VQLQ) at 1 year in the immunotherapy group compared with 8% in the control group. Mean VQLQ at the end of treatment was 5.84 in the immunotherapy group and 4.53 in the

TABLE 16 Quality of Life RCTs: trial and patient descriptives

	Trial 1			Trial 2
	Oude Elberink 2001[82]	**Oude Elberink 2002[83]**	**Oude Elberink 2006[84]**	**Oude Elberink 2009[87]**
Methods				
Design	Randomised, open-label, controlled parallel group trial	Randomised, open-label, controlled parallel group trial	Randomised, open-label, controlled parallel group trial	Randomised, open-label, controlled parallel group trial
Participants				
Country	The Netherlands	The Netherlands	The Netherlands	The Netherlands
Age range	Not stated	Adults (18–65 years)	Adults (18–65 years)	Adults (≥ 18 years)
Total *n*	101	74	94	29
Treatment group; loss to follow-up	50; not clear	36 (16 men); 2	47; 0	15 (9 men); 0
Control group; loss to follow-up	51; not clear	38 (18 men); 3	47; 1	14; 1
Species of insect venom(s) to which participants were allergic	Yellow jacket	Yellow jacket	Yellow jacket	Yellow jacket
Inclusion criteria	History of systemic reaction to yellow jacket sting and 'sensitised to yellow jacket venom'	History of one or more anaphylactic reactions after yellow jacket stings and positive SPT or serum IgE test	History of one or more anaphylactic reactions after yellow jacket stings and positive SPT or serum IgE test	One or more dermal reactions following yellow jacket stings and positive SPT or serum IgE test
Exclusion criteria	Not stated	Beta-blocker therapy or if there was a need to carry an EpiPen for other reasons, mastocytosis or serious medical or surgical illness and pregnancy	Beta-blocker therapy or if there was a need to carry an EpiPen for other reasons, mastocytosis or serious medical or surgical illness and pregnancy	Beta-blocker therapy or if there was a need to carry an EpiPen for other reasons, mastocytosis or serious medical or surgical illness and pregnancy
Interventions				
Treatment	Subcutaneous injections of VIT	Subcutaneous injections of VIT	Subcutaneous injections of VIT	Subcutaneous injections of VIT
VIT	Pharmalgen/Alutard (ALK Abelló)	Pharmalgen/Alutard (ALK Abelló)	Pharmalgen/Alutard (ALK Abelló)	Pharmalgen/Alutard (ALK Abelló)
Duration	1 year	1 year	1 year	1 year
Updosing	Modified semi-rush protocol over approximately 6-week period	Modified semi-rush protocol over approximately 6-week period	Modified semi-rush protocol over approximately 6-week period	Modified semi-rush protocol over approximately 6-week period
Maintenance dose	100 µg every 6 weeks	100 µg every 6 weeks	100 µg every 6 weeks	100 µg every 6 weeks
Control	EpiPen	EpiPen	EpiPen	EpiPen
Outcomes		Systemic reaction to accidental insect sting	Systemic reaction to accidental insect sting	
	Quality of life using a 7-point health-related QoL score	Quality of life assessment using VQLQ at 1 year	Quality of life assessment using BOT questionnaire at 1 year	Quality of life assessment using VQLQ at 1 year
Notes	May be some overlap with people in Oude Elberink 2002[83] and 2006[84] publications			

control group. In an abstract publication[82] the same research group reported a mean difference in QoL score change of a 0.96-point improvement on a 1–7 scale after 1 year of yellow jacket immunotherapy in 50 people compared with a 0.37-point deterioration in a control group of 51 people, all of whom had a history of systemic allergic reaction. A further publication[83] by the same research group in 69 people with a history of systemic reaction to yellow jacket sting reported that 74% had a significant improvement in QoL score (an increase of at least 0.5 points in VQLQ) at 1 year with immunotherapy compared with 9% in the control group. Mean VQLQ at the end of treatment was 4.35 in the immunotherapy group and 2.90 in the control group. A meta-analysis of the two studies for the outcome change in VLQL over time significantly favoured VIT over EpiPen (test for overall effect: $z = 36.25$ $p < 0.00001$).

Acceptability of treatment

The studies of Oude-Elberink *et al.*[82–84,87] reported patient views of the burden of treatment in both VIT and control arms using a 7-point scale in which a score of 1–3 was classed as a 'positive' view of treatment and a score of 4–7 as negative or neutral view of treatment. In their 2006 study[84] of people with a history of systemic reaction to yellow jacket sting, 44/47 (94%) immunotherapy-treated people had a positive overall assessment of their treatment after 1 year compared with 22/46 (48%) people in the control group ($p < 0.001$); similarly, in their 2009 study[87] of people with a history of LLR to yellow jacket sting, 93% of immunotherapy-treated people and 42% of those in the control group had a positive overall assessment of their treatment at 1 year.

Summary of clinical evidence

Pharmalgen venom immunotherapy studies: comparative

- Nine studies of PhVIT were identified for inclusion in the review; none of the study comparators was a non-VIT intervention.
- One study compared PhVIT with non-PhVIT; the others compared PhVIT with PhVIT.
- Four of the included studies were RCTs and five were quasi-experimental studies.
- None of the studies was carried out in the UK.
- Dosing protocols and administration protocols of PhVIT varied across studies.
- Where re-sting data were available, the rate of systemic reactions ranged from 0.0%[40,44,45] to 36.4%[49] and the timing of re-sting varied across studies.
- Systemic reactions were reported at rates of between 0.0% and 38.1% and none was fatal.
- None of the included studies reported QoL data.

Pharmalgen venom immunotherapy studies: non-comparative

- Seventeen non-comparative studies of PhVIT were identified for inclusion in the review.
- Reported rates of systemic reactions following re-sting ranged from 0.0% to 32.7%; 12 studies reported re-sting data before completion of VIT.
- Post-PhVIT systemic reaction rates ranged from 2.0% to 12.5%.
- None of the included studies reported QoL data.

Health-related quality of life

- QoL not reported in any PhVIT study.
- Two RCTs looked at QoL in people receiving a combination of PhVIT and Alutard VIT (crossover trial) versus EpiPen.
- Data showed that QoL of people receiving VIT improved more than those receiving an EpiPen.

Non-Pharmalgen venom immunotherapy studies: comparative

- Two systematic reviews and one meta-analysis assessed the clinical effectiveness of VIT versus non-VIT; none included any trials of PhVIT.
- All three studies concluded that VIT was effective in reducing systemic reactions to re-stings when compared with non-VIT interventions.

Discussion of clinical results and key issues

The aim of this clinical review was to evaluate the clinical effectiveness and cost-effectiveness of PhVIT in preventing future systemic reactions to bee and wasp venom in venom-sensitised people. To achieve this aim, comparisons were sought between PhVIT and any comparator (i.e. non-PhVIT and other non-VIT such as AAIs, HDAs and advice on the avoidance of bee and wasp stings).

No studies comparing PhVIT with non-VIT interventions were identified. Our search of the clinical effectiveness literature identified nine trials for inclusion in the review. Five clinical trials compared PhVIT with PhVIT (different doses and administration protocols) and four studies compared PhVIT with non-PhVIT. Several RCTs have been published comparing VIT with non-VIT interventions; however, none of these studies has used PhVIT. The current PhVIT literature is therefore limited to RCTs ($n = 4$) and quasi-experimental studies ($n = 5$) comparing different methods of administering PhVIT, different PhVIT dosing protocols and other non-PhVIT. Cohort studies reporting ARs to PhVIT and/or the effectiveness of PhVIT in reducing systemic reactions to subsequent re-stings have also been published; 17 non-comparative studies of PhVIT were identified for inclusion in the systematic review.

The results of this review have been limited by the decision problem set by NICE, which is focused on the use of PhVIT. Only studies that include PhVIT as the intervention of interest were therefore included in the systematic review. Not only are there very few published studies of PhVIT but the AG is very much aware that the nine comparative studies included in the systematic review do not accurately reflect, in terms of updosing and/or maintenance programmes, the dosing and administration protocols described in terms of the EU licence and may or may not reflect current UK clinical practice.

The quality of the included clinical trials was poor; all of the trials were small, with none including > 65 participants (range 6–65), and none was carried out in the UK. The authors of the included studies did not describe the method of randomisation used and there were imbalances in the rates of dropout between arms in all but one study.[49] There was heterogeneity among studies in the outcomes reported, the timing of re-stings, the type and length of treatment and the proportion of people being re-stung. Differences were also found among studies in maintenance dosing protocols. Health outcomes were measured at between 2 weeks and 5 years of maintenance therapy, thus making accurate comparison of data between studies difficult. The quality of the non-comparative studies was not assessed by the AG.

Venom immunotherapy with PhVIT carries with it a significant risk of systemic allergic reaction, with ARs reported in up to 38% of those treated in studies included in this review. However, these ARs were treatable and transient, and none was fatal.

Fatal sting anaphylaxis is estimated to occur in between two and nine individuals in the UK each year,[15] and because of the rarity of this outcome it is therefore not possible to conclude from the data presented in either the current review or previous systematic reviews[33,71,72] whether PhVIT prevents fatal sting anaphylaxis.

Because of the low occurrence of FS, the clinical effectiveness of VIT is generally assessed by SC, that is, the number of subsequent re-stings in controlled circumstances that lead to systemic ARs. Of the eight included studies reporting re-sting rates, three[32,40,49] reported FS, with the proportion of people being stung ranging from 24% to 60%. This clinical evidence suggests that there may be a degree of protection following PhVIT against systemic reaction to subsequent stings, as the systemic reaction rates in these studies following (field) re-sting ranged from 0.0% to 36.4%, which is lower than those rates reported in 'natural history' studies of untreated people. However, unless all patients are re-stung (FS), true assessment of clinical effectiveness is uncertain.

The non-comparative studies generally support the results of the comparative studies in terms of rates of ARs to PhVIT and reductions in systemic reactions following re-sting.

Only one study[83] was identified that compared a combination of PhVIT/Alutard with a non-VIT comparator (EpiPen); the study's main outcome was QoL and limited re-sting data were reported by the authors. It is not therefore possible to directly report on the clinical effectiveness of PhVIT versus EpiPen.

Two systematic reviews[33,72] and a meta-analysis[71] have concluded that VIT is effective in preventing future systemic reactions to venom in venom-allergic people; however, these studies included all types of VIT and it may not be possible to generalise the findings of these reviews to PhVIT because of differences in venom extracts and concentrations and differences in administration methods. The AG notes that venom products for use in VIT are manufactured by several different companies, and some companies produce more than one venom product.

It was not possible for the AG to undertake meta-analyses or a MTC of PhVIT versus non-PhVIT because of the small number of published RCTs and the lack of head-to-head studies available.

The AG is of the opinion that there are limited clinical data to support the use of PhVIT in the treatment of patients with a history of type 1 IgE-mediated systemic allergic reactions to bee and/or wasp venom. Whether or not the results of the clinical review are generalisable to the UK population is unknown as current clinical practice in the UK with PhVIT is varied. Clinical experts have advised the AG that PhVIT is always tailored to the needs of the individual as specified in the SmPC,[31] which means that it may be inappropriate to focus on a single standardised programme of PhVIT. Interpretation of the clinical effectiveness data assessing PhVIT is problematic because of discrepancies in timing and delivery (FS vs SC) of re-sting.

Other systematic reviews[33,72] comparing VIT with non-VIT indicate that VIT may be more effective than non-VIT in the treatment of patients with a history of allergic reaction to bee and/or wasp venom.

Chapter 4

Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

A systematic review of the economic literature was conducted to identify the existing evidence assessing the cost-effectiveness of PhVIT for the treatment of bee and wasp venom allergy. The search strategy shown in *Chapter 3* was used to identify the relevant studies for inclusion in the review. Three studies were identified; two were full papers[90,91] and one was in abstract format.[92] None of the studies compared PhVIT with AAIs, HDAs or avoidance advice, the studies were USA based and costs were expressed in US dollars. The AG was unable to apply any systematic review evaluation checklist to the identified studies and therefore brief summaries of each study are reported below.

The study by Bernstein *et al.*[90] was a 10-year observational study that reported the safety of using rapid VIT compared with modified rush VIT for people with Hymenoptera anaphylaxis. In the study, patient mean age was 36.6 years; ten and four people received single honey bee and wasp VIT, respectively, and eight people were injected with three different venoms at the same time (honey bee, wasp and mixed vespids). The paper showed that the use of rapid VIT was safe and time saving for people to reach the dose for maintenance phase compared with modified rush VIT. A cost analysis was conducted and indicated that rapid VIT is cheaper than modified rush VIT mainly because of reduced inpatient costs.

The study by Shaker[91] in 2007 was a cohort simulation study that evaluated prophylactic self-injectable adrenaline alone for the prevention of fatalities in mild childhood venom anaphylaxis. The cost-effectiveness analysis assumed that the baseline annual risk of venom fatality rate was 0.44 per 100,000 persons, and the estimated incremental cost-effectiveness ratio (ICER) was US$469,459 per life-year saved and therefore not cost-effective. Sensitivity analyses were conducted to explore alternative scenarios. When the fatality rate reached 2.2 per 100,000 persons at risk, the ICER was US$97,146 per life-year saved and self-injectable adrenaline appeared to be cost-effective; self-injectable adrenaline was increasingly cost-effective with higher fatality rates. Age variation was also explored in the sensitivity analysis; the therapy became more expensive as the cohort aged, with the ICER remaining well above the usual thresholds even for a cohort of 3-year-olds (US$459,645).

The study by Brown *et al.*[92] was published in abstract format and reported only the cost-effectiveness analysis of VIT used as cure and prevention in children experiencing severe anaphylaxis. A Markov model was used taking into account clinical likelihood, QALYs saved, reduced deaths and costs in US dollars; however, very limited data were available in the abstract. The paper concluded that VIT was cost-effective when it was used for risk reduction (US$7876 per life-year saved) and cure (US$2278 per life-year saved) in patients with a history of severe venom anaphylaxis at a greater risk of severe reactions.

Independent economic assessment

The results of the systematic review of cost-effectiveness literature revealed that there were no published economic evaluations relevant to the decision problem set by NICE. The manufacturer of PhVIT did not submit any clinical effectiveness or cost-effectiveness evidence to NICE. The AG developed a de novo economic model designed specifically to compare the cost-effectiveness of PhVIT with the cost-effectiveness of currently available NHS interventions in people with a history of type 1 IgE-mediated systemic allergic reactions to bee and wasp venom.

Overview of Assessment Group model

An overview of the AG's de novo economic model is given in *Table 17*.

TABLE 17 Key characteristics of the AG's economic model

Attribute	Economic model developed by the AG
Decision problem	The model has been structured to match the decision problem defined by NICE
Intervention	PhVIT (the model assumes that 92% of people receive conventional updosing and 8% use modified rush)
	The economic model considered PhVIT + HDA + AAI as the technology of interest as PhVIT is typically administered in combination with HDA + AAI
Comparator(s)	Comparators included according to NICE scope: HDA, AAI, avoidance advice only
	The economic model considered (1) HDA + AAI and (2) avoidance advice only as the two treatment alternatives of interest (based on clinical opinion)
Population	Individuals with previous systemic reactions to bee and/or wasp venom as well as positive test results for specific IgE antibodies
	Average age of 37 years is applied in the base case and a range of 5–55 years is explored in sensitivity analyses. Gender is not considered a significant parameter in the economic model because of its lack of impact on clinical effectiveness and cost; this assumption is tested in the sensitivity analysis
Type of model	1-year cohort decision tree model, which can be extrapolated to have a horizon of multiple years. The only changes are reductions in the size of the cohort at the end of each year as a result of sting-related death or death from other causes
Perspective costs	Costs from *NHS Reference Costs*[93] and PSSRU[94] are used
Drug costs	Drug costs from BNF 61[95] are applied:
	Pharmalgen bee venom: £54.81 (updosing pack) and £63.76 (maintenance pack)
	Pharmalgen was venom: £67.20 (updosing pack) and £82.03 (maintenance pack)
Economic evaluation	Cost-effectiveness analysis
Time horizon	Base case assumes a 10-year horizon while 5, 15, 20 and 25 years are explored in the sensitivity analysis
Outcome measure	QALYs
Discount rate	An annual rate of 3.5% is applied to both costs and health effects in the base case; 0% and 5% discount rates are applied in scenario analysis
Subgroup analysis	'High Risk of Sting Patients' and 'PhVIT Anxiety QoL Improvement' (which assumes that PhVIT is not effective at reducing systemic reactions to sting compared with HDA and AAI but does improve QoL) are the only two subgroups considered
Sensitivity analysis	Sensitivity of several model parameters is tested (see *Table 25*)
Scenario analysis	Several model scenarios are explored (see *Table 26*)

BNF, *British National Formulary*; PSSRU, Personal Social Services Research Unit.

Methods

Economic model

The economic model is constructed as a 1-year cohort decision tree that can be extrapolated to have a horizon of multiple years with the only changes being a reduction in the size of the cohort at the end of each year as a result of sting-related death or death from other causes. The average age of the cohort increases with the time horizon of the model with all-cause mortality rates changing as the average age of the cohort increases.[96] Development of a Markov model was not appropriate for disease modelling of the decision problem. To illustrate, with the exception of death, there is no transition into a state that results in changes to the key parameters, for example being stung does not change the probability of experiencing a systemic reaction from future stings.

The available evidence for the key pathway parameters (likelihood of sting, resulting systemic reaction under different treatment arms and the likelihood of death following systemic reaction) is weak. As such, construction of probability distributions around these parameters was not feasible. Instead, a deterministic model was produced using the best available estimates with sensitivity and scenario analyses employed to test the impact of changing the parameters within plausible ranges.

A schematic of the first year of the model for PhVIT + AAI + HDA is shown in *Figure 2*. The schematic for subsequent years is identical with the exception that the updosing phase of VIT is no longer present and after PhVIT has stopped the maintenance phase ends. The model then simplifies into the number of stings per patient per year with resulting systemic reactions and the number of deaths from other causes. For the other treatment arms the model is essentially this simplified version of the intervention arm. The cohort is defined as 1000 patients who receive a full course of PhVIT; any extra costs due to non-adherence to treatment are considered implicitly if maintenance continues for 5 years rather than 3 years as described in the sensitivity analysis.

Treatment options to be evaluated

To provide evidence on treatment pathways we sent out 97 electronic questionnaires to immunology clinicians in allergy clinics in the UK to gather information to inform the economic modelling. The survey and summary results are presented in *Appendix 5*. This survey identified that approximately 97% ($n = 200$) of people receiving PhVIT in the responding clinics were provided with an emergency kit that included an AAI and sometimes a HDA.

The intervention of interest is not considered to be PhVIT in isolation but rather PhVIT in combination with an emergency kit of an AAI and a HDA. The emergency kit is assumed to be provided to the patient during PhVIT treatment and for the lifetime of the patient after treatment has ended. The comparators of interest are (1) an emergency kit of an AAI and a HDA or (2) avoidance advice. It is assumed that avoidance advice is provided to all people regardless of receipt of PhVIT or an emergency kit.

Treatment pathways were determined through reviewing the included evidence on effectiveness of PhVIT in *Chapter 3*, a published audit of allergy clinics in the UK,[14] published guidelines[97] and our own survey (for results see *Appendix 5*).

For the PhVIT + AAI + HDA base case, the patient pathway is assumed to start after the individual has been assessed to be suitable for PhVIT. There are two phases to PhVIT – updosing and maintenance. During PhVIT an individual may experience local and systemic ARs. As the cost and QoL considerations for anything but systemic reactions are considered to be zero

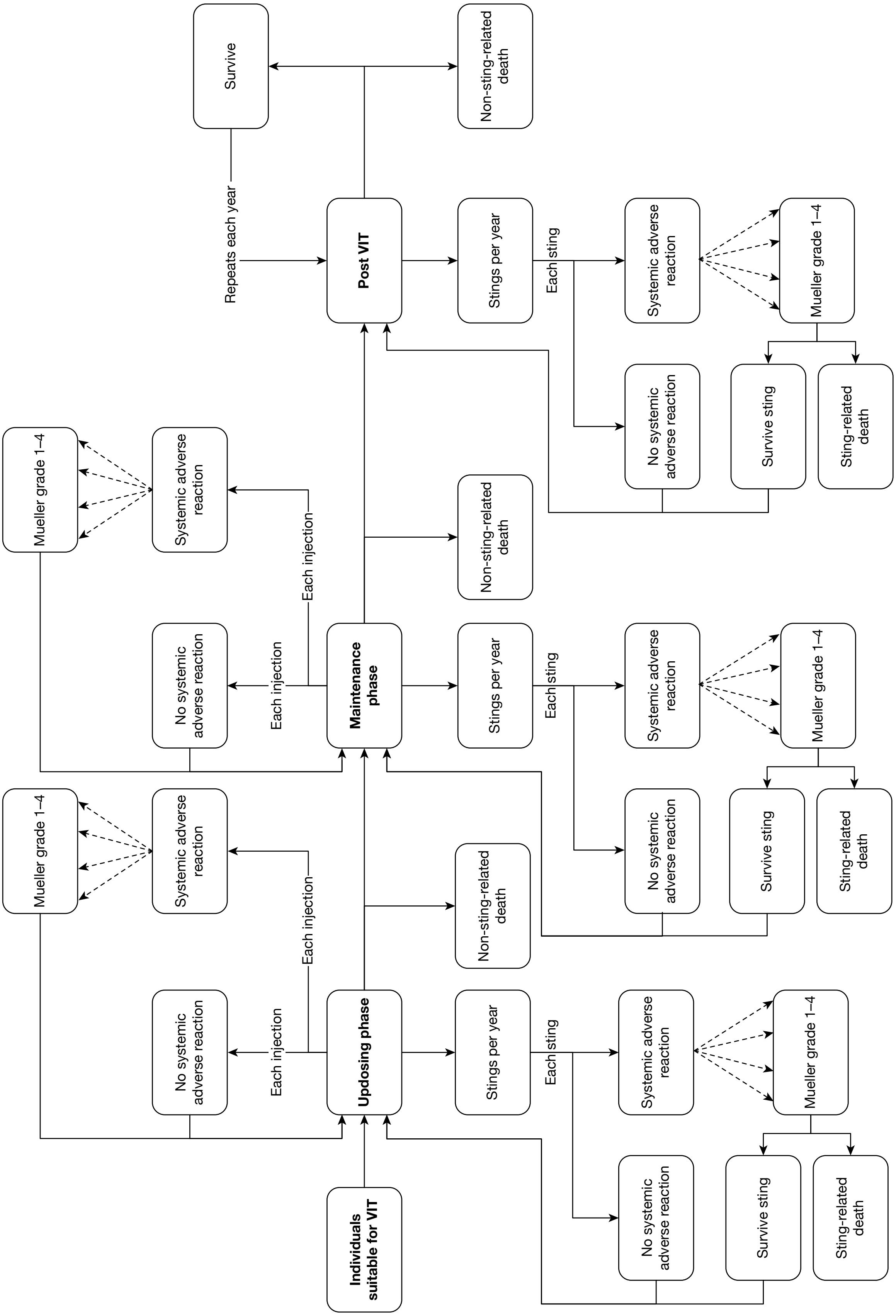

FIGURE 2 The AG's de novo economic model in the first year.

(discussed below), the pathway and model consider only systemic ARs by Mueller grade[50] (details of Mueller grade can be found in *Table 1*). The cost of treatment of ARs is assumed to vary by Mueller grade.

The patient pathway assumes that each patient will experience an average number of sting events per year during or after PhVIT. A proportion of these stings result in systemic reactions of one of the four Mueller grades. A proportion of the grade 4 systemic reactions can result in death. There is also a probability that each year a patient can die as a result of causes unrelated to his or her sting allergy, which is dependent on the age of the patient.

Patient population

The patient population considered includes people who would be considered for PhVIT as a result of their previous systemic reaction to bee and/or wasp sting and who have positive test results for specific IgE antibodies. This reflects both the licensed indication and the study populations described in the available effectiveness evidence.

The average age of people starting PhVIT is taken from our survey of clinicians in UK allergy clinics. The survey was returned by 32 out of 97 clinics (33.0%), of which 16 responded that they used PhVIT. In these clinics approximately 200 people commence PhVIT for wasp and/or bee sting each year.

For simplicity of completion of the survey, an estimate of the percentage of PhVIT patients starting in the clinic was requested for three age bands. Assuming that people were on average in the middle of each age band (aged 50 years in the 40+ band), a simple average age across responding clinics was estimated to be 37 years. This age is comparable to the average age reported in the trials included in the effectiveness review shown in *Table 8*. Sensitivity analysis was used to explore how the age of the individual when starting PhVIT influenced results, with a range between 5 and 55 years being explored.

Evidence from published studies suggests that the majority of people undertaking PhVIT are male. In the base case 80% of people are assumed to be male. As effectiveness and cost are not linked to gender, and age-related QoL norms vary only marginally by gender, it was not anticipated that this would have a significant bearing on results. To test this assumption, two scenarios were created: one in which all people were male ('100% male') and one in which all people were female ('100% female').

Model parameters

The choice of parameters and their values used in the model is based on the available published literature, discussion with UK clinicians and the results of the short economics survey of UK allergy clinics (see *Appendix 5*).

Annual number of stings for people in receipt of Pharmalgen venom immunotherapy

The model requires an estimate of the annual number of times an individual receiving PhVIT will be stung. No data were available from the UK, but six studies[32,40,49,83,98,99] identified in the literature search did contain data on FS during/following treatment with VIT. These studies provided detailed information on the number of FS events over a specified time period and included more than 10 people in each study. Other studies, notably observational studies, did provide information on FS but either were too small (≤ 10 people) or did not provide a specific length of follow-up over which the FS occurred. Findings from the six included studies are summarised in *Table 18*.

TABLE 18 Field sting data during/following treatment with VIT

Study	Country	No. of people	No. of people with re-stings	No. of years	Stings per year per person
Haye 2005[98]	Norway	315	201	5	0.128
Roesch 2008[99]	Germany	146	65	6.5	0.068
Oude Elbrink 2002[83]	Netherlands	148	2	1	0.014
Cadario 2004[40]	Italy	45	11	3	0.081
Patriarca 2008[32]	Italy	41	13	2	0.159
Thurnheer 1983[49]	Switzerland	40	22	3	0.183
Total		735	314	4.09 (weighted average)	0.095

None of the studies listed above is significantly methodologically stronger than the others and as such a simple pooling of the studies through a weighted average was used to generate an average number of stings per year (0.095); this rate compares favourably to the rates of FS reported by Cadario[40] (see *Chapter 3,* Clinical effectiveness). In the base case this value (0.095) is used. Sensitivity analysis varies the annual number of stings between lowest and highest published rates (0.014–0.183). The lower value addresses the issue that bee and wasp stings are not separated in the above data and that no evidence was found in the review detailing how people with wasp allergy react with bee sting and vice versa. If people allergic to one of the venoms are no more likely to have an allergic reaction to another venom from a different insect then the reference rate of sting used in the base case in the economic model may overestimate the actual rate and so the number of stings to which PhVIT people could have an allergic reaction to could be lower than in the base case.

Findings from these studies and from the observational studies indicated that there were people who experienced multiple stings. For example, although Kochuyt and Stevens[60] did not provide detailed information on length of follow-up, as this varied, the study found that 17 people suffered 213 bee stings during follow-up, whereas 18 people had no FS during follow-up. This could be explained by differential follow-up periods, but could also suggest that there are some people undergoing VIT who are at significantly higher risk of sting than others. This is supported by the fact that one of the factors in considering suitability for PhVIT is that an individual has an occupation or lifestyle that substantially increases their risk of sting.

A subgroup analysis ('High Risk of Sting Patients') was used to explore how people with substantially increased rates of sting affected the model findings. This subgroup has a base number of five stings per year with sensitivity analysis exploring the impact of 1–10 stings per year.

Systemic adverse reactions due to Pharmalgen venom immunotherapy

Systemic ARs due to PhVIT are included in the model as the likelihood of systemic AR following each PhVIT injection. Non-systemic ARs are not included in the base case as evidence from the effectiveness review suggests that local reactions, even if large, are short-lived and, based on discussion with clinical experts, do not incur any cost beyond the occasional use of topical or oral antihistamines. In a scenario analysis ('PhVIT Local Adverse Reactions'), we explored the impact of ignoring local reactions by assuming that 25%, 50%, 75% and 100% of post-injection ARs results in local reactions that require the administration of an antihistamine cream.

Evidence from studies described in *Chapter 3* states that the rate of systemic ARs per patient due to PhVIT is between 0% and 38.1% during treatment. However, only two papers provided the

dose risk of systemic reaction. During the updosing phase, Golden *et al.*[44] suggests a dose risk of systemic ARs of 1.6%, and a rate of 2.6% is taken from Cadario *et al.*[40] A pooled estimate across people within these trials suggests a dose risk of systemic AR during updosing of 2.0%, and this is used in the base case. Sensitivity analysis explores rates between 0% and 2.6%; the model has therefore explored what happens with higher or lower plausible values for systemic ARs no matter the reason for the increase/decrease (e.g. if there are more/fewer systemic ARs with bee PhVIT compared with wasp PhVIT).

No studies were found that reported any dose risk leading to systemic AR during the maintenance phase. However, Haye and Dosen[98] in a cohort study of 315 people receiving VIT found that 138 people had a systemic AR during the updosing phase and 59 during the maintenance phase. Insufficient detail was provided to calculate the number of injections to which this related. However, our base case assumes that over 3 years with a 4-week interval at maintenance and a 12-injection updosing phase (conventional protocol) there are approximately three times as many injections during maintenance as updosing. If the same updosing to maintenance injection ratio is applied in the model as described in the Haye and Dosen[98] study, 7.8 systemic ARs would occur during updosing for every one during maintenance. Applying this ratio to our base-case dose risk of systemic ARs during updosing suggests a dose risk during maintenance of 0.26%, and this is used in the model base case. A scenario analysis assumes a dose risk in maintenance that is equal to that in updosing ('Equal AE risk Updosing/Maintenance') and sensitivity analysis explores dose risk values in maintenance of 0–1%.

Thurnheer *et al.*'s[49] is the only study that provides information on the grade of systemic AR. This study reported that 75% of systemic ARs are grades 1–2 and 25% grades 3–4. Data on sting systemic reaction in people without VIT (*Table 19*) suggest that only a very small percentage of systemic reactions are grade 4 (1.1%). As such, we assumed that grade 1–2 reactions are split evenly between grades so in the base case grade 1 and grade 2 reactions are each 37.5% of the total.

Scenario analysis explored 100% of reactions being grade 1 ('ARs all Grade 1') and all of the grade 3/4 reactions being grade 4 ('25% ARs Grade 4').

Death due to PhVIT was not reported in any published study we identified and was assumed to be zero in the base case and was not varied in either sensitivity analysis or scenario analysis.

Systemic reactions due to stings

The model requires estimates of systemic reaction due to a sting for the three treatment arms: PhVIT + HAD + AAI versus HAD + AAI versus avoidance advice only.

For avoidance advice only, although the risk of sting may be reduced (which is accounted for by looking at the rate of sting in people who have received PhVIT – all of whom are assumed to have been given vespid sting avoidance advice), the rate of systemic reaction following sting is assumed to be equal to that of allergic people suitable for PhVIT but with no treatment.

Bilo *et al.*[12] report repeat anaphylactic risk rates following sting, assuming an episode in the past, of between 60% and 79%. This appears to be a lifetime risk rather than a per-sting risk. Reisman[100] reported the results of a survey of 220 people who had not received VIT but who had experienced a systemic reaction to sting in the past and had received a second sting since the first event. There were 124 of these people who had a systemic reaction on second sting. This suggests that the probability of systemic reaction in people with previous history of systemic reaction following sting but without PhVIT is 56.4% per sting, and this is used as the base-case value for the avoidance advice arm.

The grade of systemic reaction following sting without VIT is taken from a survey by Roesch *et al.*[99] in Germany (see *Table 19*).

The risk of systemic reaction following PhVIT was calculated by pooling the sting data from the available trial data described in *Chapter 3*. The pooled data suggest that of 337 people stung following PhVIT there were 22 systemic reactions, a rate of 6.5% per sting; from the data available it was not possible to estimate a more accurate systemic reaction rate per sting as the systemic reaction rates are reported at different times in PhVIT studies. This rate is supported by the evidence from the observational studies included in *Chapter 3* (see *Observational studies of Pharmalgen*). In sensitivity analysis the rate of systemic reaction explored following PhVIT ranges from 5% to 15%.

Although some authors report effectiveness of 100%, these studies are small and, given that other studies have found systemic reactions with PhVIT, the balance of evidence does not support suggesting 100% effectiveness for PhVIT in stopping systemic reactions. Evidence that effectiveness declines over time is mixed so in the base case it is assumed that there is no decline in effectiveness over time. A scenario analysis assumes that effectiveness declines smoothly from 5% at the end of therapy year 1 to 15% at 10 years following the end of therapy ('Declining VIT Effectiveness').

Evidence on effectiveness of PhVIT suggests that the severity of systemic reaction following sting is reduced with PhVIT, but trials that actually reported the grade of systemic reaction were too small to establish the actual impact on grade.

The survey by Roesch *et al.*[99] that provided grade of systemic reaction to sting for people before VIT also provided the grade of systemic reaction for the same people following sting after having received VIT (see *Table 19*). Although these are observational rather than trial data, in the absence of more robust data it is the best evidence available for use in the model.

High-dose antihistamine is given as an emergency treatment following a sting to reduce the possibility and severity of systemic reaction. The results of our survey found that clinicians advise the use of AAI following a sting only if symptoms of systemic reaction occur. Therefore, AAI can only reduce the severity of systemic reaction. However, for both HDA and AAI there is no published evidence to support the use of these interventions in the treatment of systemic allergic reactions.[101,102] Effectiveness therefore has to be assumed. For simplicity, in the base case, HDA is assumed to be 25% as effective as VIT at reducing the likelihood of systemic reaction, meaning that the risk of systemic reaction is 43.9% with no reduction in severity of reaction. AAI is assumed to reduce the number of grade 3 and grade 4 systemic reactions by half of the reduction with VIT with these reactions evenly distributed between grade 1 and grade 2 reactions, but AAI does not reduce the possibility of systemic reaction.

TABLE 19 Percentage of people with different grades of systemic reaction

Grade	Systemic reaction following a sting without VIT (%)	Systemic reaction following a sting with VIT (%)
1	6.5	38.5
2	80.3	54.0
3	12.1	7.5
4	1.1	0

The addition of AAI and HDA to PhVIT is assumed to not alter the effectiveness of stopping or reducing the severity of systemic reaction compared with PhVIT alone.

As these assumptions are without an evidence base, it is important that scenario analysis is used to explore how important these assumptions are to model findings. Therefore, a scenario is used in which AAI + HDA is assumed to be no more effective than avoidance advice only, that is, they make no difference to the likelihood or severity of systemic reaction following sting ('AAI + HDA No Systemic Reaction Effectiveness'). A separate scenario analysis assumes that AAI + HDA are as effective at reducing the likelihood and severity of systemic reaction as PhVIT, although an increase in QoL through reduced sting anxiety with PhVIT is introduced. This is discussed further in the section on QoL in the model.

Local reactions to sting are assumed to be trivial in terms of both cost and QoL impact and so are excluded from the model.

Deaths following sting

Deaths following sting are rare in the UK (and the rest of the world) so making an estimate of the death rate following sting is difficult. Although deaths due to sting are recorded, it is not known how many of these people received VIT or how many sting events they relate to.

To provide an estimate of sting death rate, an indirect approach was taken based upon the findings from Pumphrey and Pumphrey.[103] The survey reported an average of 20 deaths due to allergic anaphylaxis (all causes) per year in the UK. Hospital episode statistics (HES)[104] data suggest that there are approximately 1600 inpatient episodes due to anaphylaxis each year. Combining these facts suggests a death rate following anaphylaxis (which we assume in the model to be a Mueller grade 4 reaction) of 1.25%. This rate is used in the model in the base case by assuming that death from allergic anaphylaxis is independent of the allergen.

As the probability of grade 4 reaction with PhVIT is assumed to be 0% then, by default, the death rate with PhVIT due to bee/wasp sting is assumed to be 0%.

With no published range of fatality rates following sting, sensitivity analysis undertaken around this parameter explores the effect of the value being 50% higher and lower than in the base case.

Quality of life

The model estimates the number of deaths and life-years under each treatment arm over the time horizon chosen. The life-years are adjusted to calculate QALYs by using age-dependent European Quality of Life-5 Dimensions (EQ-5D) Weighted Heath Status Index population norms published by the University of York.[105]

Evidence[83,87] presented in *Chapter 3* shows that fear of sting in some people not receiving VIT reduces QoL and this is at least partly negated by PhVIT. However, no evidence is available to support this finding using a validated utility measure such as EQ-5D.[105] As such, in the base case no change in utility due to anxiety is assumed. Having a systemic reaction could potentially impact on QoL and different severities of reaction could impact on QoL differently. Unfortunately, there is no evidence on utility levels during a systemic reaction, and as such the QoL differences resulting from the number of systemic sting reactions in different treatment arms are not included in the model. This means that any health benefits from VIT are entirely due to its effectiveness in reducing systemic reactions from sting and resulting deaths.

A separate subgroup analysis assumes that fear of sting does affect the utility of some people and that VIT reduces this anxiety and so negates this loss in QoL ('VIT Anxiety QoL Improvement').

The survey of EQ-5D norms[105] by the University of York suggested that a level 2 'anxiety/depression' health state induces a detriment to utility of 0.07 per year. A level 2 interference with 'usual activities' health state induces a utility decrement of 0.036. The actual reduction would not make a significant difference to the findings of the economic model, but provides an indication of the likely scale of the positive benefit from PhVIT.

The actual reduction in utility per person per year is unlikely to exceed 0.106 in total if the fear of sting both causes a reduction in utility due to anxiety and interferes with usual activities. As a cautious estimate we assume that the actual reduction in utility due to fear of sting is approximately 40% of the potential 0.106 per person per year maximum and that this is alleviated by PhVIT by approximately 40%. This means that having PhVIT increases utility by 0.01 per person per year.

This can be interpreted as a cautious estimate of the impact of PhVIT on utility. Sensitivity analysis explores increases in utility from PhVIT of between 0.004 and 0.04 (10–100% of assumed decrease in utility due to anxiety) per person per year.

As stated previously, a separate scenario analysis explores the cost-effectiveness of PhVIT assuming that it is not effective at reducing systemic reaction to sting compared with AAI + HDA but does improve utility ('PhVIT Anxiety QoL Improvement Only').

Cost of treatment and health states

The model requires estimates of the costs of treatment in the different intervention arms as well as health-care costs in different health states, specifically from systemic ARs to PhVIT and systemic reactions to sting.

To produce these estimates a range of unit costs is applied to resource use. The resources considered in the model and the unit costs are provided in *Table 20*.

Cost of drugs and drug administration

Following published clinical guidelines,[97] administration of PhVIT was assumed to include the use of a syringe and a prophylactic HDA, the time involved in a pre-injection health check, venom injection preparation and post-injection observation (this has been defined as individuals

TABLE 20 Resources and unit costs used in the model

Resource	Unit		Unit cost (£)	Source
A&E attendance	Per attendance		103	*NHS Reference Costs*[93] (code: TA and EMSNA)
Inpatient stay	Per day		350	*NHS Reference Costs*[93] (code: WA16Y)
AAI (EpiPen)	Per injector		28.77	BNF 61[95]
Ampoule of adrenaline	Per 1 ml ampoule		0.57	BNF 61[95]
Syringe and needle	Per syringe/needle		0.10	Assumed
HDA	Per dose		0.14	BNF 61[95] (average of four most commonly used HDAs)
Allergy clinic nurse specialist	Per minute		1.07	PSSRU[94]
Pharmalgen bee venom	Per kit	Initial pack	54.81	BNF 61[95]
		Maintenance pack	63.76	BNF 61[95]
Pharmalgen wasp venom	Per kit	Initial pack	67.20	BNF 61[95]
		Maintenance pack	82.03	BNF 61[95]

BNF, *British National Formulary*; PSSRU, Personal Social Services Research Unit.

staying in the consulting room with specialists to be seen if any immediate reactions manifest). No published information was available on the actual resource usage of these individual elements so values were assumed by the AG and then verified by a consultant in an allergy clinic.

The model assumes that bee, wasp, and bee plus wasp PhVIT are equally effective. However, the cost of PhVIT for these treatments varies. Our survey of UK allergy clinic clinicians suggested that approximately 23% of people are bee allergic, 70% of people are wasp allergic and 7% are both. These proportions are used in our base case but scenario analysis explores the difference in findings if people are 100% bee allergic, 100% wasp allergic or 100% both.

According to the manufacturer's SmPC,[31] conventional updosing is carried out weekly for 12 weeks with one injection per visit. A modified rush protocol is made up of 16 injections over a period of 7 weeks. The published allergy clinic survey suggests that 92% of people receive conventional updosing and 8% use modified rush. These values are used in the model and scenario analysis is used to explore the importance of the type of protocol ('100% Conventional' and '100% Modified Rush').

In the base case the maintenance phase is assumed to be 3 years following updosing. This is varied in the sensitivity analysis between 3 years and 5 years. The interval between injections during the maintenance phase is 4 weeks, as per available guidelines, but sensitivity analysis explores the impact of intervals of between 5 weeks and 8 weeks.

The resources used and costs associated with PhVIT administration are shown in *Table 21*.

The emergency kit is assumed to comprise a HDA and an AAI. The AAI is assumed to be EpiPen and to have a shelf life of 18 months, after which a new one is issued. The HDA in the emergency kit is assumed to be replaced annually. Avoidance advice is assumed to constitute a 60-minute consultation with a nurse specialist at a cost of £64 from PSSRU.[94] As these costs are added equally to all three intervention arms, the actual cost incurred should make no difference to the results of the incremental analysis and so no sensitivity analysis was performed around these values.

Treatment of systemic adverse reactions to Pharmalgen venom immunotherapy

For local ARs to PhVIT the costs of treatment are considered to be trivial, involving the administration of an antihistamine cream or ice pack. The model focuses on systemic reactions.

No data were available describing the resources used to treat systemic ARs; therefore assumptions were made and then checked with an allergy clinic clinician. In the base case we assume that in

TABLE 21 Resource use and cost of administering PhVIT

Resource	Unit	Usage (sensitivity analysis)	Cost (£)
Prophylactic HDA	Per visit	1 dose	0.14
Pre-injection health check (nurse specialist time)	Per visit	15 minutes (10–20 minutes)	16 (10.67–21.33)
Venom injection preparation (nurse specialist time)	Per dose	5 minutes (3–7 minutes)	5.33 (3.20–7.47)
Post-injection observation (nurse specialist time)	Per dose	3 minutes (2–4 minutes)	3.20 (2.13–4.27)
PhVIT costs updosing	Updosing phase	1 kit	68.19[a]
PhVIT costs maintenance	Per injection	Quarter of a kit	20.57

a Cost differs slightly from costs in *Table 20* because a mix of bee and wasp venom is assumed.

all cases of systemic AR to PhVIT an HDA would be given and an ampoule of adrenaline drawn and administered by a nurse. The clinician suggested that in all cases of systemic AR people would be observed closely for at least 30 minutes following emergency treatment. It is assumed that all grade 4 systemic reactions result in close observation by a nurse for 60 minutes and 50% of people require a hospital inpatient stay for overnight observation. The resource use associated with systemic ARs is provided in *Table 22*. Scenario analysis explores the cost of systemic reaction that is 50% higher ('50% Higher Systemic AR Cost') and 50% lower ('50% Lower Systemic AR Cost') and a scenario analysis also explores the impact of no grade 4 systemic reactions resulting in an inpatient stay ('No Admissions Due to Systemic Adverse Reactions').

Treatment of systemic reactions to sting

Resource use and costs related to systemic reactions to sting are displayed in *Tables 23* and *24*.

It was considered that all individuals experiencing a systemic sting reaction visit the A&E department regardless of treatment arm. This is confirmed by our survey, in which we asked

TABLE 22 Resource use and costs due to systemic AR to PhVIT

	Grades 1–3		Grade 4	
	Resource use	Cost (£)	Resource use	Cost (£)
Antihistamine	1 dose	0.14	1 dose	0.14
Adrenaline	1 ampoule	0.57	1 ampoule	0.57
Needle/syringe for adrenaline	1	0.10	1	0.10
Observation time in unit (nurse specialist time)	30 minutes	32.00	60 minutes	64.00
Inpatient stay (1 day)	0% of patients	0.00	50% of patients	175.00
Total cost		32.81		239.81

TABLE 23 Resource use and costs due to systemic reactions to sting for patients in PhVIT + AAI + HDA and AAI + HDA arms

	Grade 1		Grade 2		Grade 3		Grade 4	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
A&E visit	100% of patients	103	100% of patients	103	100% of patients	103	100% of patients	103
Inpatient stay	0% of patients	0	10% of patients	35	30% of patients	105	50% of patients	175
Antihistamine	1 dose	0.14	1 dose	0.14	1 dose	0.14	1 dose	0.14
EpiPen	1	28.77	1	28.77	1	28.77	1	28.77
Total cost		131.91		166.91		236.91		306.91

TABLE 24 Resource use and costs due to systemic reactions to sting for patients in avoidance advice-only arm

	Grade 1		Grade 2		Grade 3		Grade 4	
	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)	Resource use	Cost (£)
A&E visit	100% of patients	103	100% of patients	103	100% of patients	103	100% of patients	103
Inpatient stay	0% of patients	0	10% of patients	35	30% of patients	105	50% of patients	175
Antihistamine	1 dose	0.14	1 dose	0.14	1 dose	0.14	1 dose	0.14
Adrenaline	1 ampoule	0.67	1 ampoule	0.67	1 ampoule	0.67	1 ampoule	0.67
Total cost		103.81		138.81		108.81		178.81

for avoidance advice given to people by clinicians should they be stung and all said that those experiencing a systemic reaction to sting are told to attend A&E. We assume that all people are able to attend A&E without the need for ambulatory care, which we accept potentially acts as a deflator to the actual cost of treating systemic reactions. However, no data were available on the number of people being stung and requiring paramedic assistance.

For people with an emergency kit, the model assumes that all people with a systemic reaction would use the AAI and HDA. For people receiving avoidance advice only, adrenaline is administered via ampoule in the A&E department.

There is a risk of delayed anaphylactic shock with sting and we assume that a proportion of people with systemic reactions would be observed overnight in hospital as an inpatient. We have no data on the likelihood of an inpatient stay so we asked for clinician advice on likely values for this parameter. In the base case the model assumes that 50% of those with a grade 4 systemic reaction would be held overnight for observation; it is also assumed that 30% of those with a grade 3 reaction, 10% with a grade 2 reaction and no-one with a grade 1 reaction would be held overnight for observation.

Scenario analysis explores the cost of systemic reaction that is 50% higher ('50% Higher Systemic Sting Treatment Cost') and 50% lower ('50% Lower Systemic Sting Treatment Cost'). Scenario analysis is also used to explore the impact of no inpatient stays regardless of grade of systemic reaction ('No Systemic Reaction Inpatient Stay') and 100% stay for those with a grade 4 systemic reaction ('100% Grade 4 Systemic Reaction Inpatient Stay').

Time horizon

In the base case the time horizon is 10 years. This was chosen as there is evidence that PhVIT is still effective up to 10 years after maintenance but no studies could be found that had looked at periods beyond this. Results over 5, 15, 20 and 25 years are also estimated based upon the assumption that PhVIT is equally effective over all of these periods.

Discount rate

Discount rates of 3.5% per annum are applied to both costs and benefits in the base case. Scenario analysis is used to explore the impact of no discount rate for costs and benefits and a discount rate of 5% per annum.

Other model assumptions

There are several assumptions made to make the model tractable that have not previously been mentioned.

The efficacy of bee and wasp PhVIT is assumed to be the same in terms of reducing the probability and severity of systemic reaction following sting.

Adverse reactions per dose and efficacy of PhVIT are assumed to be independent of the type of updosing phase used or length of maintenance phase (provided the maintenance phase is at least 3 years as suggested by the available evidence).

In the clinical effectiveness literature identified through the systematic review, there was no mention of ARs related to AAIs and HDAs; therefore, ARs are assumed to be zero. If there are significant ARs to either AAIs or HDAs then the costs of systemic reaction to sting are likely to be higher than we have suggested in the model. This is explored in sensitivity analysis by raising the costs of systemic reactions to sting by 50%.

Model validation

Internal validation of Assessment Group model

During model construction the algorithms within the model were checked using extreme value analysis for parameters to ensure that results generated were within acceptable bounds. To verify the accuracy of the model, key algorithms within the model were checked by an independent statistician. On completion, the model was assessed and validated by a team of external economists and statisticians.

External validation of Assessment Group model

The model was also cross-checked by an external consultant. The economic model was checked for functionality, clarity, accuracy, consistency and validity. Validation of calculated parameters within the model was carried out where possible against observational studies; however, given that this is a de novo economic model, it was not possible for the external consultant to conduct validation regarding final results.

Model parameters and values used in the base case, sensitivity analysis and scenario analysis

Table 25 summarises the parameters that can vary within the model and the values applied in the base case and sensitivity analyses.

Several scenario analyses were undertaken and these are summarised in terms of the difference in parameters from the base case (*Table 26*).

Results

For the hypothetical cohort of 1000 patients, the total number of systemic ARs to PhVIT, number of stings, severity of systemic reactions to sting, sting-related deaths, total life-years and QALYs over 10 years for each treatment arm for the base case and the two subgroups ('High Risk of Sting Patients' and 'PhVIT Anxiety QoL Improvement') are shown in *Table 27*.

The total costs for the hypothetical 1000-patient cohort in terms of intervention costs, treatment costs for ARs to PhVIT and treatment costs for systemic reactions following sting in the base case and two subgroups are provided in *Table 28*.

The incremental cost between the three treatment arms, incremental QALYs and cost per QALY of PhVIT + AAI + HDA compared with the two treatment alternatives for the base case and two subgroups for a 1000-patient cohort are shown in *Tables 29–31* respectively.

Under the base-case assumptions over 10 years, PhVIT + AAI + HDA generates an additional 0.00011 and 0.00029 QALYs per patient compared with AAI + HDA and avoidance advice respectively. This is at an additional cost of £2029 and £2185 per patient compared with AAI + HDA and avoidance advice respectively. The ICER of PhVIT + AAI + HDA is therefore £18,065,527 per QALY gained compared with AAI + HDA and £7,627,835 per QALY gained compared with avoidance advice.

For the 'High Risk of Sting Patient' subgroup, at five stings per year, the reduction in costs from systemic reactions to sting over 10 years because of PhVIT outweighs the VIT treatment costs. As PhVIT also generates additional QALYs by reducing sting deaths for this subgroup, PhVIT + AAI + HDA dominates the alternatives.

The subgroup analysis that allows for QoL changes as a result of sting anxiety and the use of PhVIT estimates that PhVIT + AAI + HDA generates an additional 0.0850 and 0.0852 QALYs

TABLE 25 Base-case and sensitivity analysis model values

Parameter	Base-case values (sensitivity analysis)
No. of stings per year for PhVIT patients	0.095 (0.014–0.183)
No. of stings per year for subgroup 'High Risk of Sting Patients'	5 (1–10)
Pre-injection health check (nurse specialist time)	15 (10–20) minutes
Venom injection preparation (nurse specialist time)	5 (3–7) minutes
Post-injection observation (nurse specialist time)	3 (2–4) minutes
Proportion of PhVIT doses leading to systemic AR	Updosing: 0.02 (0–0.026)
	Maintenance: 0.0026 (0–0.01)
Grade of systemic AR due to VIT dose	Grade 1: 37.5%, grade 2: 37.5%, grade 3: 21.9%, grade 4: 3.1%
Proportion of stings that lead to systemic reaction (advice only)	0.56
Grade of systemic reaction following sting (advice only)	Grade 1: 6.5%, grade 2: 80.3%, grade 3: 12.1%, grade 4: 1.1%
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	0.065 (0.05–0.15)
Grade of systemic reaction following sting (PhVIT + AAI + HDA)	Grade 1: 38.5%, grade 2: 54.0%, grade 3: 7.5%, grade 4: 0.0%
Proportion of stings that lead to systemic reaction (AAI + HDA)	0.439
Grade of systemic reaction following sting (AAI + HDA)	Grade 1: 9.8%, grade 2: 83.6%, grade 3: 6.05%, grade 4: 0.55%
Probability of death following grade 4 systemic reaction to sting	0.0125 (0.00625–0.01875)
Percentage of people using conventional updosing	92%
Length of maintenance phase	3 (3–5) years
Length of intervals between doses during maintenance	4 (4–12) weeks
Systemic sting reactions with inpatient stay	
Grade 1	0%
Grade 2	10%
Grade 3	30%
Grade 4	50%
QoL decrement due to anxiety of sting and impact on normal activities	0
QoL decrement in subgroup 'PhVIT Anxiety QoL Improvement'	Reduction in QoL due to fear of sting: 0.04 per annum
QoL increment due to reduction in anxiety with VIT	0
QoL increment in subgroup 'PhVIT Anxiety QoL Improvement'	Increase in QoL due to VIT: 0.01 per annum (0.004–0.04)
Age starting VIT	37 (5–55) years
Discount rate (costs and benefits)	3.5% (0–5%)

per patient compared with AAI + HDA and avoidance advice respectively. The incremental cost per patient is the same as in the base case. The ICER for the subgroup with sting anxiety that is partially alleviated with PhVIT + AAI + HDA is therefore £23,868 per QALY gained compared with AAI + HDA and £25,661 per QALY gained compared with avoidance advice only.

Sensitivity analysis

The results of the sensitivity analysis for the base case and two subgroups are presented in *Tables 32–34*, respectively, and show the impact on the ICER when parameters are varied; PhVIT + AAI + HDA is compared with the two treatment alternatives.

Scenario analysis

The impact of changes on the ICERs for PhVIT + AAI + HDA, under the different scenarios presented, compared with the alternative treatments is provided in *Tables 35–37* for the base case, 'High Risk of Sting Patients' subgroup and 'PhVIT Anxiety QoL Improvement' subgroup respectively.

TABLE 26 Model values in scenario analysis

Scenario	Parameters changed	Value taken (sensitivity analysis)
5-, 15-, 20-, 25-year time horizon	Time horizon	5, 15, 20, 25 years
100% male	Gender	Male 100%
100% female	Gender	Male 0%
100% bee	Percentage of people receiving bee PhVIT only	100%
100% wasp	Percentage of people receiving wasp PhVIT only	100%
100% bee/wasp	Percentage of people receiving both bee and wasp PhVIT	100%
100% conventional updosing	Percentage of people on conventional updosing protocol	100%
PhVIT local ARs	Inclusion of costs for local ARs to PhVIT	Add £0.84 to the cost per PhVIT injection in both phases
Equal AR risk updosing/maintenance	Dose risk of systemic reaction during maintenance phase	Risk of systemic AR in maintenance phase 2.0%
ARs all grade 1	Mueller grade of systemic ARs	Grade 1 systemic ARs 100%
25% ARs all grade 4	Mueller grade of systemic ARs	Grade 4 systemic ARs 25%
50% higher systemic AR cost	Cost of all grades of systemic ARs to PhVIT	Cost of all grades of systemic ARs to PhVIT + 50%
50% lower systemic AR cost	Cost of all grades of systemic ARs to PhVIT	Cost of all grades of systemic ARs to PhVIT − 50%
50% higher systemic sting treatment cost	Cost of all grades of systemic reactions to sting	Cost of all grades of systemic reactions to sting + 50%
50% lower systemic sting treatment cost	Cost of all grades of systemic reactions to sting	Cost of all grades of systemic reactions to sting − 50%
No admissions due to systemic ARs to PhVIT	Percentage of grade 4 systemic ARs resulting in admission	0%
Declining PhVIT effectiveness	Risk of systemic reaction from sting with PhVIT	5% at year 1 following the end of maintenance increasing by 1% per annum to 15% after 10 years following maintenance
No systemic reaction inpatient stay	Proportion of people requiring an inpatient stay after systemic sting reaction	0%
100% grade 4 systemic reaction inpatient stay	Proportion of people requiring an inpatient stay after a grade 4 systemic sting reaction	100%
AAI + HDA no systemic reaction effectiveness	Risk and severity of systemic reaction	Same as advice only intervention
PhVIT anxiety QoL improvement only	QoL age-related norms, sting systemic reactions with AAI + HDA	Reduction in QoL due to fear of sting 0.04 per annum, increase in QoL due to PhVIT 0.01 per annum (0.004–0.04). Risk and severity of systemic reaction following sting with AAI + HDA equal to that with PhVIT + AAI + HDA
Best case	All parameters varied in base-case sensitivity analysis	Values chosen that make PhVIT the most cost-effective (lowest cost/QALY)
Worst case	All parameters varied in base-case sensitivity analysis	Values chosen that make PhVIT the least cost-effective (lowest cost/QALY)

Summary of economics evidence

- No published economic evaluations relevant to the decision problem were identified by the systematic review of cost-effectiveness studies.
- The manufacturer of PhVIT did not submit any supporting clinical effectiveness or cost-effectiveness evidence to NICE.
- The AG developed a de novo economic model to compare PhVIT with currently available NHS treatments in patients with a history of type 1 IgE-mediated systemic allergic reaction to bee and/or wasp venom.

TABLE 27 Health-related outcomes for the base case and two subgroups

Treatment effect	Treatment arm	Base case	High risk of sting patients	PhVIT anxiety QoL improvement
Systemic AR to PhVIT	PhVIT + AAI + HDA	450	450	450
Grade 1		169	169	169
Grade 2		169	169	169
Grade 3		99	99	99
Grade 4		14	14	14
Stings	PhVIT + AAI + HDA	943	49,639	943
	AAI + HDA	943	49,606	943
	Advice only	943	49,554	943
Systemic reaction to sting	PhVIT + AAI + HDA	61	3223	61
	AAI + HDA	414	21,777	414
	Advice only	528	27,750	528
Grade 1	PhVIT + AAI + HDA	24	1239	24
	AAI + HDA	41	2134	41
	Advice only	34	1804	34
Grade 2	PhVIT + AAI + HDA	33	1742	33
	AAI + HDA	346	18,206	346
	Advice only	424	22,283	424
Grade 3	PhVIT + AAI + HDA	5	242	5
	AAI + HDA	25	1318	25
	Advice only	64	3358	64
Grade 4	PhVIT + AAI + HDA	0	0	0
	AAI + HDA	2	120	2
	Advice only	6	305	6
Sting-related deaths	PhVIT + AAI + HDA	0.00	0.00	0.00
	AAI + HDA	0.03	1.50	0.03
	Advice only	0.07	3.82	0.07
Total life-years	PhVIT + AAI + HDA	9908.0	9908.0	9908.0
	AAI + HDA	9907.8	9899.8	9907.8
	Advice only	9907.6	9887.1	9907.6
Total QALYs	PhVIT + AAI + HDA	7626.6	7626.6	7371.9
	AAI + HDA	7626.5	7620.7	7286.9
	Advice only	7626.3	7611.5	7286.7

Note: totals may not add up to sum of component parts due to rounding.

TABLE 28 Costs of intervention and systemic reactions to sting for 1000 patients in the base case and subgroups for the different treatment arms

Cost element	Treatment arm	Base case (£)	High risk of sting patients (£)	PhVIT anxiety QoL improvement (£)
Treatment costs	PhVIT + AAI + HDA	2,299,327	2,299,223	2,299,327
	AAI + HDA	228,330	228,228	228,330
	Advice only	64,000	64,000	64,000
Systemic AR	PhVIT + AAI + HDA	17,637	17,637	17,637
Systemic reaction to sting	PhVIT + AAI + HDA	9764	513,919	9764
	AAI + HDA	69,591	3,660,233	69,591
	Advice only	77,285	4,060,750	77,285
Total costs	PhVIT + AAI + HDA	2,326,729	2,830,778	2,326,729
	AAI + HDA	297,921	3,888,461	297,921
	Advice only	141,285	4,124,750	141,285

TABLE 29 Incremental costs, QALYs and ICERs for PhVIT + AAI + HDA under the base case

	AAI + HDA	Avoidance advice only
Incremental cost	£2,028,808	£2,185,444
Incremental QALYs	0.11	0.29
Cost per QALY (ICER)	£18,065,527	£7,627,835

TABLE 30 Incremental costs, QALYs and ICERs for PhVIT +AAI + HDA for the 'High Risk of Sting Patients' subgroup

	AAI + HDA	Avoidance advice only
Incremental cost	–£1,057,682	–£1,293,972
Incremental QALYs	5.91	15.06
Cost per QALY (ICER)	–£179,020	–£85,903

TABLE 31 Incremental costs, QALYs and ICERs for PhVIT + AAI + HDA for the 'VIT Anxiety QoL Improvement' subgroup

	AAI + HDA	Avoidance advice only
Incremental cost	£2,028,808	£2,185,444
Incremental QALYs	85.00	85.17
Cost per QALY (ICER)	£23,868	£25,661

TABLE 32 Impact of sensitivity analysis on the ICER of PhVIT + AAI + HDA compared with different treatment arms in the base case

Parameter	Cost per QALY vs AAI + HDA (£)	Cost per QALY vs advice only (£)
No. of stings per year (0.014–0.183)	9,122,183 to 125,668,803	3,846,558 to 53,122,895
Pre-injection health check (nurse specialist time)	15,724,577 to 20,406,478	6,710,254 to 8,545,415
Venom injection preparation (nurse specialist time)	17,115,470 to 19,015,585	7,255,442 to 8,000,228
Post-injection observation (nurse specialist time)	17,590,498 to 18,540,556	7,441,638 to 7,814,031
Proportion of PhVIT doses leading to systemic AR (updosing phase)	17,979,460 to 19,098,328	7,594,099 to 8,032,661
Proportion of PhVIT doses leading to systemic AR (maintenance phase)	17,994,545 to 18,267,553	7,600,012 to 7,707,023
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	18,045,462 to 18,179,228	7,619,970 to 7,672,402
Probability of death following grade 4 systemic reaction to a sting	36,130,899 to 12,043,736	15,255,509 to 5,085,277
Length of maintenance phase	18,065,527 to 27,331,818	7,627,835 to 11,259,936
Length of intervals between injections during maintenance phase	18,065,527 to 7,903,259	7,627,835 to 3,644,538
Age starting PhVIT	16,924,162 to 21,390,991	7,148,354 to 9,015,238
Discount rate (costs and benefits)	15,129,011 to 19,487,889	6,452,674 to 8,196,637

- In the AG's base case, PhVIT + HDA + AAI reached an ICER of £18,065,527 per QALY gained compared with AAI + HDA.
- In the AG's base case, PhVIT + HDA + AAI reached an ICER of £7,627,835 per QALY gained compared with avoidance advice only.
- In the AG's base case the results of the sensitivity analyses and scenario analyses showed that the results of the economic evaluation were robust for every plausible change in parameter made.
- The AG's 'High Risk of Sting Patients' subgroup analysis showed that the PhVIT + HDA + AAI dominates both AAI + HDA and avoidance advice only.

TABLE 33 Impact of sensitivity analysis on the ICER of PhVIT + AAI + HDA compared with different treatment arms in the 'High Risk of Sting Patients' subgroup

Parameter	Cost per QALY vs AAI + HDA	Cost per QALY vs advice only
No. of stings per year (1–10)	£1,234,283 to –£355,512	£511,546 to –£160,398
Pre-injection health check (nurse specialist time)	Dominates	Dominates
Venom injection preparation (nurse specialist time)	Dominates	Dominates
Post-injection observation (nurse specialist time)	Dominates	Dominates
Proportion of PhVIT doses leading to systemic AR (updosing phase)	Dominates	Dominates
Proportion of PhVIT doses leading to systemic AR (maintenance phase)	Dominates	Dominates
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	Dominates	Dominates
Probability of death following grade 4 systemic reaction to a sting	Dominates	Dominates
Length of maintenance phase	Dominates	Dominates
Length of intervals between injections during maintenance phase	Dominates	Dominates
Age starting PhVIT	Dominates	Dominates
Discount rate (costs and benefits)	Dominates	Dominates

TABLE 34 Impact of sensitivity analysis on the ICER of PhVIT + AAI + HDA compared with different treatment arms in the 'PhVIT Anxiety QoL Improvement' subgroup

Parameter	Cost per QALY vs AAI + HDA (£)	Cost per QALY vs advice only (£)
No. of stings per year (0.014–0.183)	23,189 to 24,495	24,853 to 26,409
Pre-injection health check (nurse specialist time)	20,775 to 26,961	22,574 to 28,748
Venom injection preparation (nurse specialist time)	22,613 to 25,124	24,408 to 26,914
Post-injection observation (nurse specialist time)	23,241 to 24,496	25,035 to 26,287
Proportion of PhVIT doses leading to systemic AR (updosing phase)	23,755 to 25,233	25,547 to 27,023
Proportion of PhVIT doses leading to systemic AR (maintenance phase)	23,775 to 24,135	25,567 to 25,927
Proportion of stings that lead to systemic reaction (PhVIT + AAI + HDA)	23,842 to 24,019	25,634 to 25,811
Probability of death following grade 4 systemic reaction to sting	23,883 to 23,853	25,702 to 25,620
Length of maintenance phase	23,868 to 36,111	25,661 to 37,880
Length of intervals between injections during maintenance phase	23,868 to 10,442	25,661 to 12,261
Age starting PhVIT	23,711 to 24,697	25,497 to 26,510
Discount rate (costs and benefits)	21,065 to 25,140	22,875 to 26,925
Age-related QoL norm (decreases by 0.04), QoL norm with PhVIT (increases by 0.004 to 0.04)	5973 to 59,558	6431 to 63,845

- The AG's 'VIT Anxiety QoL Improvement' subgroup analysis showed that PhVIT + HDA + AAI vs HDA + AAI had an ICER of £23,868 per QALY gained.
- The AG's 'VIT Anxiety QoL Improvement' subgroup analysis showed that PhVIT + HDA + AAI vs avoidance advice only had an ICER of £25,661 per QALY gained.

Discussion of economics results and key issues

No relevant economic evaluations of PhVIT versus any comparator were identified from the systematic review of cost-effectiveness literature. The manufacturer did not submit any clinical effectiveness or cost-effectiveness evidence to NICE, which means that the AG did not have any additional data from the manufacturer. The AG developed a de novo economic model to answer the decision problem set by NICE.

TABLE 35 Incremental cost-effectiveness ratios for PhVIT + AAI + HDA compared with the different treatment arms under various scenarios for the base case

Scenario	Cost per QALY vs AAI + HDA[a] (£)	Cost per QALY vs advice only[a] (£)
5-year time horizon	58,112,401 (+321.68)	23,728,992 (+311.08)
15-year time horizon	9,475,380 (–47.55)	4,112,030 (–46.09)
20-year time horizon	6,158,390 (–65.91)	2,733,478 (–64.16)
25-year time horizon	4,549,884 (–74.81)	2,056,752 (–73.04
100% male	18,094,419 (+0.16)	7,639,773 (+0.16)
100% female	17,950,948 (–0.63)	7,580,491 (–0.62)
100% bee venom	16,391,486 (–9.27)	6,971,662 (–8.60)
100% wasp venom	18,034,830 (–0.17)	7,615,802 (–0.16)
100% bee/wasp venom	23,872,923 (+32.15)	9,904,156 (+29.84)
100% conventional updosing protocol	18,095,990 (+0.17)	7,639,775 (+0.16)
100% modified rush updosing protocol	17,715,201 (–1.94)	7,490,518 (–1.80)
PhVIT local ARs	18,439,612 (+2.07)	7,774,465 (+1.92)
Equal AR risk updosing/maintenance	18,540,562 (+2.63)	7,814,034 (+2.44)
ARs all grade 1	18,039,836 (–0.14)	7,617,765 (–0.13)
25% ARs grade 4	18,247,022 (+1.00)	7,698,975 (+0.93)
50% higher systemic AR cost	18,144,052 (+0.43)	7,658,614 (+0.40)
50% lower systemic AR cost	17,987,003 (–0.43)	7,597,056 (–0.40)
50% higher systemic sting treatment cost	17,799,166 (–1.47)	7,510,002 (–1.54)
50% lower systemic sting treatment cost	18,331,888 (+1.47)	7,745,668 (+1.54)
No admissions due to systemic ARs	18,043,808 (–0.12)	7,619,321 (–0.11)
Declining PhVIT effectiveness	18,087,837 (+0.12)	7,636,580 (+0.11)
No systemic reaction inpatient stay	18,185,034 (+0.66)	7,700,600 (+0.95)
100% grade 4 systemic reaction inpatient stay	18,062,700 (–0.02)	7,624,569 (–0.04)
AAI + HDA no systemic reaction effectiveness	7,002,582 (–61.24)	NA
Best-case scenario	1,449,007 (–91.98)	731,302 (–90.41)
Worst-case scenario	570,668,032 (+3058.88)	232,820,521 (+2952.25)

NA, not applicable.
a Percentage difference from base case in brackets.

Under the base case the incremental cost per QALY gained for PhVIT + AAI + HDA compared with an emergency kit of AAI + HDA is never < £1M under any scenario or any plausible values for parameters within the model. The ICER falls below £1M only when PhVIT + AAI + HDA is compared with avoidance advice and the most optimistic scenario for PhVIT + AAI + HDA is considered; however, this ICER still exceeds £700,000 per QALY gained.

As scenario analysis explored extreme values when assumptions had to be made – such as in the costs associated with treating a systemic reaction following sting – this finding can be considered robust and unlikely to change if additional information were available to provide more accurate values for these assumptions. The underlying driver for this ICER is that, although PhVIT can achieve savings through reduced systemic reaction treatment costs and generate QALYs through saving lives, the likelihood of being stung and then dying from that sting is very low – even for individuals allergic to sting. The ability of PhVIT to generate QALY gains and reduce demand on NHS resources is therefore low.

The findings are considerably different for the two subgroups that are considered in our analysis. First, considering allergic individuals at high risk of sting, subgroup analysis suggests that,

TABLE 36 Incremental cost-effectiveness ratios for PhVIT + AAI + HDA compared with different treatment arms under various scenarios for the 'High Risk of Sting Patients' subgroup

Scenario	Cost per QALY vs AAI + HDA[a] (£)	Cost per QALY vs advice only[a] (£)
5-year time horizon	274,556	84,006
15-year time horizon	Dominates	Dominates
20-year time horizon	Dominates	Dominates
25-year time horizon	Dominates	Dominates
100% male	Dominates	Dominates
100% female	Dominates	Dominates
100% bee venom	Dominates	Dominates
100% wasp venom	Dominates	Dominates
100% bee/wasp venom	Dominates	Dominates
100% conventional updosing protocol	Dominates	Dominates
100% modified rush updosing protocol	Dominates	Dominates
PhVIT local ARs	Dominates	Dominates
Equal AR risk updosing/maintenance	Dominates	Dominates
ARs all grade 1	Dominates	Dominates
25% ARs grade 4	Dominates	Dominates
50% higher systemic AR cost	Dominates	Dominates
50% lower systemic AR cost	Dominates	Dominates
50% higher systemic sting treatment cost	Dominates	Dominates
50% lower systemic sting treatment cost	87,248	31,829
No admissions due to systemic ARs	Dominates	Dominates
Declining PhVIT effectiveness	Dominates	Dominates
No systemic reaction inpatient stay	Dominates	Dominates
100% grade 4 systemic reaction inpatient stay	Dominates	Dominates
AAI + HDA no systemic reaction effectiveness	Dominates	NA
Best-case scenario (fixed at five stings per annum)	Dominates	Dominates
Worst-case scenario (fixed at five stings per annum)	547,263	172,930

NA, not applicable.
a Values shown when ICER becomes positive.

under all other base-case values, at a rate of five stings per year, PhVIT + AAI + HDA reduces the number of systemic reactions to stings, and therefore total costs of systemic sting reaction, to a point that it actually costs less than the other treatment arms. Although even at this level of sting the number of deaths averted and therefore QALYs generated is low with PhVIT + AAI + HDA, as it still generates some QALYs compared with the other treatment arms its lower cost means that it dominates the other arms as a treatment option. This finding is invariant to the changes made to almost all parameters in scenario analysis and sensitivity analysis. The exceptions are if a time horizon of only 5 years is considered, treatment costs for systemic reaction are 50% lower than in the base case and the most pessimistic plausible values for all parameters in the model are chosen.

Our survey found that allergy clinics advise all people that, if stung and having signs of systemic reaction, they should attend A&E. It is therefore not plausible that this cost should be lower than we have considered. The only other cost of treatment considered that could significantly inflate the cost of treatment is inpatient care. Under the scenario of no inpatient care following sting, PhVIT + AAI + HDA still dominated.

TABLE 37 Incremental cost-effectiveness ratios for PhVIT + AAI + HDA compared with different treatment arms under various scenarios for the 'PhVIT Anxiety QoL Improvement' subgroup

Scenario	Cost per QALY vs AAI + HDA[a] (£)	Cost per QALY vs advice only[a] (£)
5-year time horizon	44,328 (+85.72)	46,126 (+79.75)
15-year time horizon	17,128 (–28.24)	18,912 (–26.30)
20-year time horizon	13,806 (–42.16)	15,582 (–39.28)
25-year time horizon	11,879 (–50.23)	13,647 (–53.18)
100% male	23,884 (+0.07)	25,677 (+0.06)
100% female	23,807 (–0.26)	25,598 (–0.25)
100% bee venom	21,657 (–9.27)	23,453 (–8.60)
100% wasp venom	23,828 (–0.17)	25,620 (–0.16)
100% bee/wasp venom	31,541 (+32.15)	33,319 (+29.84)
100% conventional updosing protocol	23,909 (+0.17)	25,701 (+0.16)
100% modified rush updosing protocol	23,406 (–1.94)	25,199 (–1.80)
PhVIT local ARs	24,363 (+2.07)	26,154 (+1.92)
Equal AR risk updosing/maintenance	24,496 (+2.63)	26,287 (+2.44)
ARs all grade 1	23,834 (–0.14)	25,627 (–0.13)
25% ARs grade 4	24,108 (+1.01)	25,900 (+0.93)
50% higher systemic AR cost	23,972 (+0.44)	25,764 (+0.40)
50% lower systemic AR cost	23,765 (–0.43)	25,557 (–0.40)
50% higher systemic sting treatment cost	23,516 (–1.47)	25,265 (–1.55)
50% lower systemic sting treatment cost	24,220 (+1.48)	26,057 (+1.54)
No admissions due to systemic ARs	23.840 (–0.12)	25,632 (–0.11)
Declining PhVIT effectiveness	23,898 (+0.12)	25,690 (+0.11)
No systemic reaction inpatient stay	24,026 (+0.66)	25,906 (+0.95)
100% grade 4 systemic reaction inpatient stay	23,865 (–0.01)	25,650 (–0.04)
AAI + HDA no systemic reaction effectiveness	23,557 (–1.30)	NA
PhVIT anxiety QoL improvement only	24,605 (+3.09)	NA
Best-case scenario (fixed at 0.01 per annum PhVIT QoL improvement)	6179 (–74.11)	7906 (–69.19)
Worst-case scenario (fixed at 0.01 per annum PhVIT Qol improvement)	47,390 (+98.55)	49,320 (+92.20)

NA, not applicable.
a Percentage difference from base case in brackets.

Assuming that all other parameters for the base case hold, the number of stings at which PhVIT + AAI + HDA would no longer dominate and incremental costs per QALY would be generated would be 3.3 stings per year compared with AAI + HDA and 3.2 stings per year compared with avoidance advice only. The number of stings per year for which PhVIT + AAI + HDA would generate an ICER of £30,000 per QALY gained is 3.1 compared with AAI + HDA and 2.8 compared with avoidance advice only. We considered a third subgroup that would combine an improvement in utility from reduction in anxiety in a population with a high risk of sting. As PhVIT + AAI + HDA dominates, assuming no improvement in QoL from receiving PhVIT, this subgroup analysis was considered unnecessary.

For people with the base-case risk of sting or lower risk of sting, keeping in mind that the base-case risk will potentially include people at significantly higher risk of sting than others and that the sting risk is a combined wasp and bee sting risk and people may not have an allergic response to both, the cost-effectiveness of PhVIT improves substantially if QALYs are generated not only by stopping sting deaths, but also through reductions in sting anxiety. The evidence on

improvement in QoL is limited but suggests that PhVIT does effectively reduce sting anxiety. Although the actual effect of this on utility as measured by a recognised survey is absent, the research by the University of York previously discussed suggests that QoL can be substantially influenced both by the individual's inability to undertake usual activities and because of anxiety.

Our analysis explored how the cost-effectiveness of PhVIT varies if fear of sting has only a small negative impact on QoL compared with the potential impact identified by the University of York research. It also assumed that PhVIT + AAI + HDA has only a small impact in negating this loss in utility. If fear of sting reduces utility by 0.04 of a QALY per annum and PhVIT improves utility by 25% of this value (0.01 of a QALY per annum), the ICERs for PhVIT + AAI + HDA are < £30,000 per QALY gained compared with AAI + HDA and avoidance advice only if all other base-case values hold. This result holds across a range of scenarios and potential plausible parameter values, even if PhVIT is assumed to be no more effective than an emergency kit of AAI + HDA at stopping and alleviating systemic reactions to sting.

The finding is somewhat sensitive to PhVIT treatment costs, most notably the length of the maintenance phase. With a maintenance phase of 5 years the ICER rises to just under £40,000 per QALY gained compared with the alternative treatments. For people requiring both bee and wasp PhVIT the ICER also rises to between £33,440 per QALY gained and £35,163 per QALY gained compared with AAI + HDA and avoidance advice only respectively.

If the reduction in utility from sting anxiety is 0.04 per annum, then for PhVIT + AAI + HDA to generate an ICER of £30,000 per QALY gained it has to negate this reduction by 0.008 per annum compared with AAI + HDA and 0.009 compared with avoidance advice only. For people receiving both bee and wasp PhVIT, the incremental increase in QoL per annum has to rise from 0.01 to 0.011 to achieve an ICER of £30,000 per QALY gained compared with both AAI + HDA and avoidance advice only.

As the treatment costs are all incurred within the first 5 years of the analysis but benefits continue to accrue past this point, the ICERs at 5 years are higher than the base-case ICERs at 10 years and continue to fall up to 25 years. As the available evidence suggests that PhVIT continues to be effective up to at least 10 years but is limited beyond this, the choice of a 10-year time horizon is in our opinion justified.

Although we consider the findings robust, there are some key weaknesses of our analysis:

- the lack of data on effectiveness of PhVIT from RCTs
- the lack of any published evidence on PhVIT + AAI + HDA versus AAI + HDA or avoidance advice only
- the absence of direct data on the number of stings in PhVIT people in the UK and the number of stings that are from bees or wasps
- the absence of direct data on the likelihood of death following sting for sting-allergic people
- the absence of robust data on the improvement in utility because of sting anxiety in allergic people.

To counter this lack of evidence and potential criticism of simplifying assumptions, substantial sensitivity and scenario analyses were used to highlight those parameters that are key to the cost-effectiveness analysis and explore the impact on the cost-effectiveness results of the intervention in question across ranges of plausible values. The final weakness is shown to be irrelevant if increases in utility from reduced sting anxiety arise through PhVIT as the findings hold even if PhVIT has no effectiveness on systemic reactions to sting.

Chapter 5

Conclusions

The current use of PhVIT in clinical practice in the NHS appears to be based on limited and poor-quality clinical effectiveness research.

The AG did not identify any studies of PhVIT that directly addressed the original decision problem set for this appraisal, i.e. to compare the use of PhVIT with the alternative treatment options of advice on the avoidance of bee and wasp venom, HDA and/or AAIs.

This lack of evidence and the need to identify data to inform the development of an economic model prompted the AG to broaden the search criteria for the systematic review in order to compare PhVIT with other PhVIT and PhVIT with non-PhVIT, to consider data from non-comparative studies of PhVIT, and to examine studies reporting the clinical effectiveness of non-PhVIT.

In general, research in the area is limited to small-scale studies that do not appear to have been carried out using robust methods, and none of the studies reported on the use of PhVIT within the UK. There is also heterogeneity in the published evidence related to the methods of PhVIT administration and length of treatment described in the trials. Therefore, conclusions regarding the clinical effectiveness of PhVIT to reduce the rate of future systemic reactions in patients with a history of bee and/or wasp allergic reaction cannot be drawn with any confidence. Available evidence indicates that sting reactions following the use of PhVIT are low and that the ARs related to treatment are minor and easily treatable.

Anxiety related to the possibility of future stings is an issue for debate, and data from studies of VIT indicate a small improvement in QoL as a result of a decrease in sting-related anxiety after VIT.

No published research on the cost-effectiveness of PhVIT or non-PhVIT was identified by the literature searches. The results of the AG's de novo base-case economic evaluation demonstrate that PhVIT + AAI + HDA compared with AAI + HDA and with avoidance advice only yield ICERs in the range of £8–18M per QALY gained. The results of extensive sensitivity and scenario analyses demonstrate that the base-case results are robust. Two subgroups were considered in the economic evaluation, and the AG concludes that use of PhVIT + AAI + HDA may be cost-effective in both groups. In the subgroup of patients at high risk of future stings (five stings per year), PhVIT + AAI + HDA dominates the alternatives. In the subgroup of patients whose QoL improves because PhVIT reduces anxiety, when PhVIT + AAI + HDA is compared with the alternatives the ICERs are in the range of £23,868–25,661 per QALY gained.

Future research

Use of PhVIT in clinical practice in the UK NHS is commonplace and it is therefore highly unlikely that placebo-controlled studies will ever be carried out. The findings of this review indicate, however, that it is necessary to identify more clearly the groups of patients most likely to

benefit from treatment and ensure that clinical practice is focused on these groups. Second, given the paucity of UK data in this area it would be informative if data could be collected routinely when VIT is administered in the NHS (e.g. rates of systemic ARs to VIT, rates of systemic reactions to bee/wasp stings).

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Juliet Hockenhull: project lead, review of clinical evidence.

Mariam Elremeli: contribution of data from ongoing Cochrane review of venom immunotherapy.

M Gemma Cherry: support of review process (clinical).

James Mahon: development of de novo economic model.

Monica Lai: development of economic model, input into all aspects of the economic review.

Jim Darroch: clinical advisor.

James Oyee: statistical analysis.

Angela Boland: support of review process (clinical and economic).

Rumona Dickson: support of review process.

Yenal Dundar: development of search strategies.

Robert Boyle: contribution of data from ongoing Cochrane review of venom immunotherapy.

All authors read and commented on draft versions of the Evidence Review Group (ERG) report.

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109. Birnbaum J, Charpin D, Vervloet D. Rapid hymenoptera venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy* 1993;**23**:226–30.

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117. Quercia O, Emiliani F, Pecora S, Burastero SE, Stefanini GF. Efficacy, safety, and modulation of immunologic markers by immunotherapy with honeybee venom: comparison of standardized quality depot versus aqueous extract. *Allergy Asthma Proc* 2006;**27**:151–8.

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120. Rerinck HC, Przybilla B, Ruff F. Venom immunotherapy (VIT) in patients with systemic mastocytosis (SM) and Hymenoptera venom anaphylaxis (HVA): safety and efficacy of different maintenance doses. *J Allergy Clin Immunol* 2009;**123**(Suppl. 2):242.

121. Rueff F, Wolf H, Schnitker J, Ring J, Przybilla B. Specific immunotherapy in honeybee venom allergy: a comparative study using aqueous and aluminium hydroxide adsorbed preparations. *Allergy* 2004;**59**:589–95.

122. Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004;**351**:668–74.

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126. Cichocka-Jarosz E, Tobiasz-Adamczyk B, Brzyski P, Lis G, Jedynak U, Pietrzyk J, *et al.* Health related quality of life (HRQoL) in Polish children treated with specific venom immunotherapy (VIT): a multicenter study. *Allergy* 2009;**64**:343.

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131. Roberts-Thomson PJ, Harvey P, Sperber S, Kupa A, Heddle RJ. Bee sting anaphylaxis in an urban population of South Australia. *Asian Pac J Allergy* 1985;**3**:161–4.

Appendix 1

Literature search strategies

TABLE 38 Search strategy for EMBASE 1980 to 2011 week 4

	Searches	Results
1	exp wasp/or exp bee/or exp hymenoptera/or exp bumblebee/or exp honeybee/or exp orchid bee/or exp stingless bee/	13,498
2	(wasp$or bees or honeybee$or bumblebee$or orchid bee$or yellow hornet$or yellow jacket$or white hornet$or poliste$).tw.	9959
3	exp hymenoptera venom/or exp bee sting/or exp bee venom/or exp wasp venom/	3382
4	((wasp$or bees) adj (venom$or sting$or hypersensitivit$or allerg$or anaphyla$or systemic reaction$)).tw.	818
5	(pharmalgen or venom immunotherapy).af.	692
6	exp pharmalgen/	84
7	or/1–4	19,103
8	or/5–6	692
9	7 and 8	518
10	limit 9 to english language	435

TABLE 39 Search strategy for Ovid MEDLINE(R) 1948 to February week 3 2011

	Searches	Results
1	exp Wasps/or exp Bees/or exp Hymenoptera/	12,580
2	(wasp$or bees or honeybee$or bumblebee$or orchid bee$or yellow hornet$or yellow jacket$or white hornet$or poliste$).tw.	8437
3	exp Wasp Venoms/or exp Bee Venoms/	5214
4	((wasp$or bees) adj (venom$or sting$or hypersensitivit$or allerg$or anaphyla$or systemic reaction$)).tw.	662
5	exp “Insect Bites and Stings”/	4448
6	or/1–5	22,197
7	(pharmalgen or immunotherapy).af.	52,392
8	exp Desensitization, Immunologic/or *Immunotherapy/or Anaphylaxis/th	19,439
9	7 or 8	57,963
10	6 and 9	1130
11	limit 10 to english language	906

TABLE 40 Search strategy for The Cochrane Library February 2011

	Searches	Results
1	MeSH descriptor **Wasps** explode all trees	7
2	MeSH descriptor **Bees** explode all trees	13
3	MeSH descriptor **Wasp Venoms** explode all trees	11
4	MeSH descriptor **Bee Venoms** explode all trees	28
5	wasp* or bees	231
6	(#1 OR #2 OR #3 OR #4 OR #5)	231

Appendix 2

Excluded studies

TABLE 41 Excluded studies with rationale

Comparing active treatments, none of which were Pharmalgen

Alessandrini AE, Berra D, Rizzini FL, Mauro M, Melchiorre A, Rossi F, *et al.* Flexible approaches in the design of subcutaneous immunotherapy protocols for Hymenoptera venom allergy. *Ann Allergy Asthma Immunol* 2006;**97**:92–7[106]

Bilo B, Severino M, Cilia M, Pio A, Casino G, Campodonico P, *et al.* Safety and tolerability of venom immunotherapy with purified extracts in comparison with nonpurified products. A randomised controlled multicentre trial in 94 patients. *Allergy* 2009;**64**:341–2[107]

Bilo MB, Severino M, Cilia M, Pio A, Casino G, Ferrarini E, *et al.* The VISYT trial: venom immunotherapy safety and tolerability with purified vs nonpurified extracts. *Ann Allergy Asthma Immunol* 2009;**103**:57–61[108]

Birnbaum J, Charpin D, Vervloet D. Rapid hymenoptera venom immunotherapy: comparative safety of three protocols. *Clin Exp Allergy* 1993;**23**:226–30[109]

Bousquet J, Fontez A, Aznar R. Combination of passive and active immunization in honeybee venom immunotherapy. *J Allergy Clin Immunol* 1987;**79**:947–54[110]

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Clayton WF, Reisman RE, Mueller U, Arbesman CE. Modified rapid venom desensitization. *Clin Allergy* 1983;**13**:123–9[112]

Elberink HO, Monchy JD, Guyatt G, Dubois A. Venom immunotherapy (VIT) improves health-related quality of life (HROL) in patients with allergic reactions following yellow-jacket stings – extended observations. *J Allergy Clin Immunol* 2001;**107**:S222[82]

Glerant JC, Martinez P, Guillaume C, Jounieaux V. Comparison of 2 maintenance doses (100 mug vs 200 mug) in Hymenoptera venom immunotherapy: influence of the maintenance close on the immunologic response. *Ann Allergy Asthma Immunol* 2005;**94**:451–6[113]

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Reisman RE, Dvorin DJ, Randolph CC, Georgitis JW. Stinging insect allergy: natural history and modification with venom immunotherapy. *J Allergy Clin Immunol* 1985;**75**:735–40[119]

Rerinck HC, Przybilla B, Ruff F. Venom immunotherapy (VIT) in patients with systemic mastocytosis (SM) and Hymenoptera venom anaphylaxis (HVA): safety and efficacy of different maintenance doses. *J Allergy Clin Immunol* 2009;**123**(Suppl. 2):242[120]

Rueff F, Wolf H, Schnitker J, Ring J, Przybilla B. Specific immunotherapy in honeybee venom allergy: a comparative study using aqueous and aluminium hydroxide adsorbed preparations. *Allergy* 2004;**59**:589–95[121]

Comparing VIT with placebo, WBE or no treatment but not Pharmalgen

Golden DB, Kagey-Sobotka A, Norman PS, Hamilton RG, Lichtenstein LM. Outcomes of allergy to insect stings in children, with and without venom immunotherapy. *N Engl J Med* 2004;**351**:668–74[122]

Hunt KJ, Valentine MD, Sobotka AK, Benton AW, Amodio FJ, Lichtenstein LM. A controlled trial of immunotherapy in insect hypersensitivity. *N Engl J Med* 1978;**299**:157–61[28]

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continued

TABLE 41 Excluded studies with rationale (*continued*)

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Economic papers but not Pharmalgen

Bernstein JA, Kagen SL, Bernstein DI, Bernstein IL. Rapid venom immunotherapy is safe for routine use in the treatment of patients with Hymenoptera anaphylaxis. *Ann Allergy* 1994;**73**:423–8[90]

Brown KF, Shaker MS, Jenkins PC, Verdi MS. A cost-effectiveness analysis of venom desensitization in children treated for cure and risk-reduction. *J Allergy Clinical Immunol* 2006;**117**:S309[92]

Shaker MS. An economic evaluation of prophylactic self-injectable epinephrine to prevent fatalities in children with mild venom anaphylaxis. *Ann Allergy Asthma Immunol* 2007;**99**:424–8[91]

Details of QoL but not RCTs

Cichocka-Jarosz E, Tobiasz-Adamczyk B, Brzyski P, Lis G, Jedynak U, Pietrzyk J, *et al.* Health related quality of life (HRQoL) in Polish children treated with specific venom immunotherapy (VIT): a multicenter study. *Allergy* 2009;**64**:343[126]

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Confino-Cohen R, Melamed S, Goldberg A. Debilitating beliefs and emotional distress in patients given immunotherapy for insect sting allergy: a prospective study. *Allergy Asthma Proc* 2009;**30**:546–51[128]

Kahan E, Ben-Moshe R, Derazne E, Tamir R. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med* 1997;**47**:273–6[129]

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Roberts-Thomson PJ, Harvey P, Sperber S, Kupa A, Heddle RJ. Bee sting anaphylaxis in an urban population of South Australia. *Asian Pac J Allergy* 1985;**3**:161–4[131]

Roesch A, Boerzsoenyi J, Babilas P, Landthaler M, Szeimies RM. [Outcome survey of insect venom allergic patients with venom immunotherapy in a rural population.] *J Dtsch Dermatol Ges* 2008;**6**:292–7[99]

Appendix 3

Included studies

RCTs

1 Golden DBK, Valentine MD, Kagey-Sobotka A, Lichtenstein LM. Regimens of hymenoptera venom immunotherapy. *Ann Intern Med* 1980;**92**:620–4[44]

2 Golden D, Valentine MD, Sobotka AK, Lichtenstein LM. Regimens of hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1979;**63**:180[41]

3 Mosbech H, Malling HJ, Biering I. Immunotherapy with yellow jacket venom. A comparative study including three different extracts, one adsorbed to aluminium hydroxide and two unmodified. *Allergy* 1986;**41**:95–103[45]

4 Müller U, Rabson AR, Bischof M, Lomnitzer R, Dreborg S, Lanner A. A double-blind study comparing monomethoxy polyethylene glycol-modified honeybee venom and unmodified honeybee venom for immunotherapy. I. Clinical results. *J Allergy Clin Immunol* 1987; **80**:252–61[47]

5 Müller U, Lanner A, Schmid P, Bischof M, Dreborg S, Hoigné R. A double blind study on immunotherapy with chemically modified honey bee venom: monomethoxy polyethylene glycol-coupled versus crude honey bee venom. *Int Arch Allergy Appl Immunol* 1985;**77**:201–3[46]

6 Quercia O, Rafanelli S, Puccinelli P, Stefanini GF. The safety of cluster immunotherapy with aluminium hydroxide-adsorbed honey bee venom extract. *J Investig Allergol Clin Immunol* 2001;**11**:27–33[48]

Non-RCTs

7 Cadario G, Marengo F, Ranghino E, Rossi R, Gatti B, Cantone R, *et al.* Higher frequency of early local side effects with aqueous versus depot immunotherapy for Hymenoptera venom allergy. *J Investig Allergol Clin Immunol* 2004;**14**:127–33[40]

8 Golden DBK, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Prolonged maintenance interval in hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;**67**:482–4[42]

9 Golden DBK, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Dose dependence of hymenoptera venom immunotherapy. *J Allergy Clin Immunol* 1981;**67**:370–4[43]

10 Patriarca G, Nucera E, Roncallo C, Aruanno A, Lombardo C, Decinti M, *et al.* Sublingual desensitization in patients with wasp venom allergy: preliminary results. *Int J Immunopathol Pharmacol* 2008;**21**:669–77[32]

11 Thurnheer U, Müller U, Stoller R. Venom immunotherapy in hymenoptera sting allergy. Comparison of rush and conventional hyposensitization and observations during long-term treatment. *Allergy* 1983;**38**:465–75[49]

Appendix 4

Quality assessment

TABLE 42 Data quality assessment

Checklist item	Cadario 2004[40]	Golden 1980[44]	Golden 1981[43]	Golden 1981[42]	Mosbech 1986[45]	Müller 1987[47]	Patriarca 2008[32]	Quercia 2001[48]	Thurnheer 1983[49]
Randomisation									
Was the randomisation method adequate?	NA	NS	NA	NA	NS	NS	NA	NS	NA
Was the allocation of treatment adequately concealed?	NA	NS	NA	NA	NS	NS	NA	NS	NA
Was the number of participants randomised stated?	NA	✓	NA	NA	✓	✓	NA	✓	NA
Baseline comparability									
Were details of baseline comparability presented?[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were the groups similar for prognostic factors?	✓	✓	✓	✓	×	✓	✓	✓	✓
Eligibility criteria and co-interventions									
Were the eligibility criteria for study entry specified?	✓	✓	✓	✓	✓	✓	✓	✓	✓
Were any co-interventions identified?	×	×	×	×	×	×	×	×	×
Blinding									
Were outcome assessors blinded to the treatment allocation?	×	×	×	×	×	NS[a]	×	×	×
Were administrators blinded to the treatment allocation?	×	×	×	×	×	NS[a]	×	×	×
Were people blinded to the treatment allocation?	×	×	×	×	×	NS[a]	×	×	×
Was the blinding procedure assessed?	×	×	×	×	×	×	×	×	×
Withdrawals									
Any unexpected imbalances in dropouts between groups? Were they explained or adjusted for?	×, NA	✓, ×	✓,	NS, NS	✓, ×	✓, ×	✓	×, NA	×, NA
Were ≥ 80% of people included in the final analysis?	✓	✓	✓	✓	×	✓	✓	✓	✓
Were reasons for withdrawals stated?	NA	✓	✓	×/✓	✓	✓	✓	NA	✓
Was an ITT analysis included? Was this appropriate? Were appropriate methods used to account for missing data?	NA	×	×	×	×	×	×	NA	×
Outcomes									
Evidence of more outcomes measured than reported?	×	×	×	×	×	×	×	×	×

NA, not applicable; NS, not stated/unclear.
a Double-blind trial but no details.

Appendix 5

Economic survey results

TABLE 43 Summary of the economic survey responses

Questions	Response
Type of clinical unit	14 from a unit in an acute hospital
	1 from a unit in a community hospital
	1 unit in a specialist hospital, no acute service
Type of individual receiving VIT in unit	12 units provide VIT only to adults
	2 units provide VIT only to children
	2 units provide VIT to children and adults
No. of new venom-allergic individuals in a typical year	Wasp venom: 9.37
	Bee venom: 3
	Both wasp and bee venom: 0.87
	Note that these are simple averages from 15 responses (one clinician did not fill in this question). No weighting was taken into account because we did not ask for the total number of individuals in each clinical unit. One provided a range of 5 to 10, and the median 7.5 was used for the average calculation
Age proportions of new individuals with severe systemic reaction to bee/wasp venom in a typical year	Under 20 years: 15%
	20–39 years: 30%
	40+ years: 54%
	These are simple averages without weighting
Treatment options prescribed to new patients with severe bee/wasp bee venom allergy	The majority of clinics provide VIT + HDA + AAI; four clinics provide VIT + AAI and 1 clinic uses VIT monotherapy only. For individuals not able to receive VIT, 10 clinics use HDA + AAI as an alternative treatment option. Very small numbers of clinics prescribe either HDA only or AAI only
Antihistamines prescribed (dosage)	Acrivastine (16 mg), acrivastine (8 mg), cetirizine (10–20 mg), fexofenadine (180 mg), piriton, loratadine (10–20 mg), chlorphenamine (8 mg)
VIT for individuals with both bee and wasp allergy	5 clinics provide VIT for the more severe allergy
	3 clinics provide VIT for both bee and wasp allergy
Advice given to people undergoing VIT should they experience re-sting	3 clinics advise use of HDA followed by AAI (if systemic reaction occurs); also advise visit to A&E
	4 clinics advise use of HDA and administration of AAI if individual has difficulty breathing or feels faint
	1 clinic advises use of HDA + steroid + AAI if systemic reaction occurs
	1 clinic advises HDA only
	1 clinic advises removal of sting and use of HDA + AAI
Most common ARs during VIT	Local reactions (mainly swelling and itching) stated by all 15 clinics
	Other common ARs include urticaria and fatigue. Less common reactions include pain, wheezing, local redness, Arthus-type reaction, anxiety tachycardia, headache, anaphylaxis and reduction in peak expiratory flow rate

Appendix 6

Data abstraction tables

TABLE 44 Dosing protocols

Study ID	Intervention	Updosing: doses and frequency
Cadario 2004[40]	Aqueous induction and aqueous maintenance	**12 doses in 8 visits (weekly), total 8 weeks** Week 1: 0.01 µg, 0.1 µg (30 minutes between); week 2: 1 µg, 2 µg (30 minutes between); week 3: 4 µg, 8 µg (60 minutes between); week 4: 10 µg, 20 µg (60 minutes between); week 5: 40 µg; week 6: 60 µg; week 7: 80 µg; week 8: 100 µg
	Depot induction and depot maintenance	**15 doses in 15 visits (weekly), total 15 weeks** Week 1: 0.02 µg; week 2: 0.04 µg; week 3: 0.08 µg; week 4: 0.2 µg; week 5: 0.4 µg; week 6: 0.8 µg; week 7: 2 µg; week 8: 4 µg; week 9: 8 µg; week 10: 10 µg; week 11: 20 µg; week 12: 40 µg; week 13: 60 µg; week 14: 80 µg; week 15: 100 µg
Golden 1980[41,44]	Slow therapy	**14 doses in 14 visits (weekly), total 14 weeks** Week 1: 0.01 µg; week 2: 0.03 µg; week 3: 0.1 µg; week 4: 0.25 µg; week 5: 1.0 µg; week 6: 2.5 µg; week 7: 5.0 µg; week 8: 10.0 µg; week 9: 20.0 µg; week 10: 30.0 µg; week 11: 40.0 µg; week 12: 60.0 µg; week 13: 80.0 µg; week 14: 100.0 µg
	Step therapy	**10 doses in 8 visits, total 11 weeks** Initial: 1, 5, 10 µg (every 30 minutes); week 1: 25 µg; week 3: 25 µg; week 5: 25 µg; week 6: 50 µg; week 8: 50 µg; week 10: 50 µg; week 11: 100 µg
	Rush therapy	**6 doses in 4 visits (every 2 weeks), total 6 weeks** Initial: 1, 5, 10 µg (every 30 minutes); week 2: 30 µg; week 4: 60 µg; week 6: 100 µg
Golden 1981[43]	50 µg maintenance	**6 doses in 6 visits (weekly), total 6 weeks** 1 µg on first day and achieving 50-µg dose after 6 weeks
	100 µg maintenance[44]	**6 doses in 4 visits every 2 weeks, total 6 weeks** Designed to achieve 100-µg dose within 6 weeks
	100 µg maintenance[28]	**12? doses in 9? visits, total 4 weeks** Designed to achieve 100-µg dose within 4 weeks
Golden 1981[42]	4-weekly maintenance a	NA
	6-weekly maintenance	NA
	4-weekly maintenance b	NA
Müller 1987[46,47]	HBV	**9 doses in 7 visits (weekly), total 6 weeks** Week 0: 0.1, 1.0, 3.0 µg; week 1: 5 µg; week 2: 10 µg; week 3: 20 µg; week 4: 40 µg; week 5: 65 µg; week 6: 100 µg
	Monomethoxy polyethylene glycol-coupled HBV	**7 doses in 5 visits (weekly), total 4 weeks** Week 0: 0.5, 5.0, 10.0 µg; week 1: 30 µg; week 2: 60 µg; week 3: 100 µg; week 4: 200 µg

continued

TABLE 44 Dosing protocols (*continued*)

Study ID	Intervention	Updosing: doses and frequency
Mosbech 1986[45]	Pharmalgen	**25 doses in 13 visits (twice weekly), total 13 weeks** >1 injection per visit initially until local swelling exceeded 5 cm in diameter 0.2, 0.4, 0.8 ml at 0.001 µg/ml concentration; 0.2, 0.4, 0.8 ml at 0.01 µg/ml concentration; 0.2, 0.4, 0.8 ml at 0.1 µg/ml concentration; 0.2, 0.4, 0.8 ml at 1 µg/ml concentration; 0.2, 0.3, 0.4, 0.6, 0.8 ml at 10 µg/ml concentration; 0.1, 0.15, 0.2, 0.3, 0.4, 0.6, 0.8, 1 ml at 100 µg/ml
	Alutard	**19 doses in 19 visits (weekly), total 19 weeks** Once a week: 0.02, 0.04, 0.08, 0.2, 0.4, 0.8, 2.0, 3.0, 4.0, 6.0, 8, 10, 15, 20, 30, 40, 60, 80, 100 µg
	Aquagen	**25 doses in 13 visits (twice weekly), total 13 weeks** >1 injection per visit initially until local swelling exceeded 5 cm in diameter 0.2, 0.4, 0.8 ml at 0.001 µg/ml concentration; 0.2, 0.4, 0.8 ml at 0.01 µg/ml concentration; 0.2, 0.4, 0.8 ml at 0.1 µg/ml concentration; 0.2, 0.4, 0.8 ml at 1 µg/ml concentration; 0.2, 0.3, 0.4, 0.6, 0.8 ml at 10 µg/ml concentration; 0.1, 0.15, 0.2, 0.3, 0.4, 0.6, 0.8, 1 ml at 100 µg/ml
Patriarca 2008[32]	Ultra-rush SCIT	**6 doses in 1 visit (every 30 minutes), total 3 hours** Day 1: 0.1, 1, 10, 20, 30, 40 µg
	Ultra-rush SLIT	**10 doses in 1 visit (every 20 minutes), total 3 hours** Dilution 1 : 10,000, 1 drop; dilution 1 : 1000, 1 drop; dilution 1 : 100, 1 drop; dilution 1 : 10, 1 drop; pure, 1 drop; pure, 2 drops; pure, 4 drops; pure, 6 drops; pure, 7 drops; pure, 10 drops
Quercia 2001[48]	Pharmalgen: cluster	**12 doses in 6 visits (every week), total 6 weeks** Week 1: 5 doses 0.01, 0.1, 1.0, 3.0, 6.0 µg (hourly); week 2: 1 dose 20.0 µg; week 3: 1 dose 40.0 µg; week 4: 1 dose 60.0 µg; week 5: 2 doses 40.0, 40.0 µg; week 6: 2 doses 50.0, 50.0 µg
	Pharmalgen: rush	**13 doses in 4 visits (every day), total 4 days** Day 1: 4 doses 0.01, 0.1, 1.0, 2.0 µg (hourly); day 2: 4 doses 4.0, 6.0, 10.0, 20.0 µg (hourly then fourth 30 minutes); day 3: 2 doses 40.0, 40.0 µg (hourly); day 4: 3 doses 60.0, 50.0, 50.0 µg (hourly)
	Depot cluster	**12 doses in 5 visits (weekly), total 5 weeks** Week 1: 4 doses 0.03, 0.1, 0.3, 1.0 µg (hourly); week 2: 2 doses 2.0, 4.0 µg (hourly); week 3: 2 doses 10.0, 20.0 µg (hourly); week 4: 2 doses 40.0, 40.0 µg (hourly); week 5: 2 doses 50.0, 50.0 µg (hourly)
Thurnheer 1983[49]	Conventional	**24 doses in 10 visits (weekly), total 10 weeks** Day 1: 0.1 ml (0.0001 µg/ml), 0.1 ml (0.001 µg/ml), 0.1 ml (0.01 µg/ml); day 8: 0.1 ml (0.1 µg/ml), 0.1 ml (1 µg/ml), 0.2 ml (1 µg/ml); day 15: 0.4 ml, 0.8 ml (1 µg/ml); day 22: 0.1 ml, 0.2 ml (10 µg/ml); day 29: 0.4 ml, 0.8 ml (10 µg/ml); day 36: 0.1 ml, 0.2 ml (100 µg/ml); day 43: 0.3 ml, 0.4 ml (100 µg/ml); day 50: 0.5 ml, 0.6 ml (100 µg/ml); day 57: 0.7 ml, 0.8 ml (100 µg/ml); day 64: 0.9 ml, 1.0 ml (100 µg/ml)
	Rush	**35 doses in 10 visits (daily), total 10 days** Day 1: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (0.0001 µg/ml); day 2: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (0.001 µg/ml); day 3: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (0.01 µg/ml); day 4: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (0.1 µg/ml); day 5: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (1 µg/ml); day 6: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (10 µg/ml); day 7: 0.1 ml, 0.2 ml, 0.4 ml, 0.8 ml (100 µg/ml); day 8: 0.4 ml, 0.5 ml, 0.6 ml (100 µg/ml); day 9: 0.7 ml, 0.8 ml (100 µg/ml); day 10: 0.9 ml, 1.0 ml (100 µg/ml)

HBV, honey bee venom; N/A, not available; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Appendix 7

Project protocol

1 TITLE OF PROJECT

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

2 TAR TEAM

Liverpool Reviews and Implementation Group (LR*i*G), 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® has had UK marketing authorisation for the diagnosis and treatment (using VIT) of allergy to bee venom (using Pharmalgen® Bee Venom) and wasp venom (using Pharmalgen® 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® 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® 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® 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 immunoglobin 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).[1]

Bee and wasp stings contain allergenic proteins. In wasps, these are predominantly phospholipase A1,[2] hyaluronidase[2] and antigen 5,[3] and in bees are phospholipase A2 and hyaluronidase.[4] 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.[5-6] Systemic allergic reactions may occur in venom-sensitive patients immediately following a sting,[7] and can vary in severity, with initially mild symptoms sometimes progressing to critical conditions within seconds.[1]

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.[8]

4.3 *Epidemiology*

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

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.[18] 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%).[19]

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,[20] and as negative skin tests can occur following recent anaphylaxis, it is recommended that tests be repeated after 1 to 6 months.[21]

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.[22-23]

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,[24] 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.[25] 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®, Adrenaclick®, Anapen® or Twinject®). 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.[26] Currently, VIT can be used with several regimes, including Pharmalgen® (manufactured by ALK Abello, and licensed in the UK), Aquagen® and Alutard SQ® (both manufactured by ALK Abello and unlicensed in the UK but licensed in some parts of Europe), VENOMENHAL® (HAL Allergy, Leiden, Netherlands, unlicensed in the UK), Alyostal® (Stallergenes, Antony Cedex, France, unlicensed in the UK), and Venomil® (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'.[27] 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,[28] and is a model for allergen-specific therapy,[29-30] with success rates (patients who will remain anaphylaxis free) being reported as more than 98% in some studies.[4, 31] 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.[27]

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® 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® Bee Venom) and wasp venom (Pharmalgen® Wasp Venom) since March 1995 (marketing authorisation number PL 10085/0004). The active ingredient is partially purified freeze dried *Vespula spp.* venom in Pharmalgen® Wasp Venom and freeze dried *Apis mellifera* venom in Pharmalgen® 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 Pharmalgen® 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 updosing. In conventional updosing, the patient receives one injection every 3-7 days. In modified rush (clustered) updosing, 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 updosing, 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 β-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 pharyngial congestion, wheezing, dyspnoea, nausea, hypotension, syncope, tachycardia or diarrhoea). [32]

4.7 *Objectives of the HTA project*

The aim of this review is to assess the clinical and cost effectiveness of Pharmalgen® 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 Pharmalgen® 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 Pharmalgen® 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: advice on the avoidance of bee and wasp venom, high-dose antihistamines, adrenaline auto-injector prescription and training
Study design	Randomised controlled trials Systematic reviews
Outcomes	Outcome measures to be considered include: number and severity of type 1 IgE-mediated systemic allergic reactions mortality anxiety related to the possibility of future allergic reactions adverse effects of treatment health-related quality of life
Other considerations	If the evidence allows, considerations will be given to subgroups of people, according to their: risk of future stings (as determined, for example, by occupational exposure) risk of severe allergic reactions to future stings (as determined by such factors as baseline tryptase levels and co-morbidities) If the evidence allows, the appraisal will consider separately people who have a contraindication to adrenaline. If the evidence allows, the appraisal will consider children separately.

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.[33-34] 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.[35] Heterogeneity between the studies will be assessed using the I^2 test.[34] 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 Pharmalgen® 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 Pharmalgen® 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.[36] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[37] 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. [37]

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. [37]

c. 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 22nd 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 Dundar
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

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:[36]

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

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We look forward to hearing from you.

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