Project title

Allergen immunotherapy in adults and children with severe hay fever: systematic review of effectiveness and economic modelling

Planned investigation

Background

'Hay fever' is the common name classically given to seasonal allergic rhinitis or rhinoconjunctivitis. This is a disorder of the nose and eyes characterised by nasal obstruction, rhinorrhoea, itching of the nose and sneezing, with itching, redness, soreness and watering of the eyes. The relative severity of these symptoms varies between patients. Symptoms are caused by an IgE-mediated inflammation of the membranes lining the nasal cavity and conjunctiva occurring in response to an allergen. Common allergens include tree or grass pollen, moulds, animal dander and house dust mite. In Britain, the main cause of allergic rhinitis is grass pollen, particularly perennial rye (*Lolium perenne*) and timothy grass (*Phleum pratense*), with symptoms peaking in June and July.[1]

The term 'hay fever' emerges from the traditional classification of allergic rhinitis into 'seasonal', 'perennial' and 'occupational' according to the time of exposure to the underlying allergen. Seasonal allergic rhinitis, or hay fever, is typically caused by a response to pollens and outdoor moulds while perennial allergic rhinitis is caused by house dust mites, animal dander and indoor moulds. In 2001 a new classification was suggested by the World Health Organisation ARIA (Allergic Rhinitis and its Impact on Asthma) Workshop.[2] This new classification relies on the measurement of the frequency and duration of symptoms (see table 1) rather than upon the timing of the presence of the allergen.

Allergic rhinitis is an extremely common disease, with estimates of worldwide prevalence being in the region of 25% of the population. Estimates of the prevalence of allergic rhinitis in the UK vary from 15–30%[3,4] although the true prevalence is difficult to ascertain because many people with symptoms self-diagnose and use over-the-counter remedies. It is believed the prevalence of seasonal allergic rhinitis is higher in children and adolescents than it is in adults, with perennial allergic rhinitis being more common in adults.[2] Allergic rhinitis tends to be more common in 'Western' developed countries.

General practice consultation rates for allergic rhinitis in England show an increase in new patients with this diagnosis year on year between 2001 and 2005. A rate of 5.57 per 1000 person years in 2001 rose

TABLE 1 ARIA classification of allergic rhinitis, 2001[2]

Intermittent Symptoms	Persistent Symptoms
<4 days / week	≥4 days / week
or	and
<4 weeks	≥4 weeks
Severity: Mild	Severity: Moderate – Severe
Normal sleep	Abnormal sleep
Normal daily activities, sport, leisure	Impairment of daily activities, sport, leisure
Normal work and school	Problems caused at work or school
No troublesome symptom	Troublesome symptoms (one or more items)

to 7.41 by 2005, an increase of 33%. At the same time there was a 41% increase in the number of prescriptions issued (antihistamines 45.5%, 'drugs used in nasal allergies' 35.5%).[5]

Allergic rhinitis is not usually a severe or life threatening disease but it can detrimentally affect school[6] and work performance[7], as well as causing social disruption to individuals who suffer from it. The economic burden of allergic rhinitis is high, both in terms of costs to the NHS and due to work days lost.[3,8]

Allergic rhinitis is an independent risk factor for asthma. Around 80% of people with asthma also have symptoms of allergic rhinitis. Studies have shown a temporal relationship – with rhinitis frequently preceding asthma.[2] Those who have allergic rhinitis are around three times more likely to get asthma than those who do not.[9]

Inflammation of the nasal membranes in allergic rhinitis can cause a worsening of asthma through various different mechanisms and so optimal treatment of rhinitis may, to some extent, improve coexisting asthma.[2]

Diagnosis of allergic rhinitis is usually clinical with a typical history being given, in the case of hay fever, of seasonal symptoms over several years. The more common symptoms of sneezing, rhinorrhoea, stuffy nose and conjunctivitis may be accompanied by others such as anosmia (loss of smell), snoring or other sleep problems, facial pain, wheezing and tightness of the chest. Diagnosis is confirmed by a skin prick test, which demonstrates an IgE mediated allergic reaction of the skin to a specific allergen. There is no widely accepted measure of the severity of nasal obstruction. In the new ARIA classification severity of allergic rhinitis is assessed through the effect the condition has on everyday functioning of the individual.

In clinical trials, the primary outcome measures generally used are symptom score and use of (rescue) medication. Symptom scoring systems vary widely across trials, and can include physician or patient self-rated questionnaires. One more common scoring system is a score from 0–3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe symptoms) for symptoms such as runny nose, blocked nose, sneezing, itchy nose, gritty feeling/red/itchy eyes and watery eyes.[10] QoL is more likely to be a secondary outcome measure. A well validated scale is the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)[11], a disease specific quality of life measure. Generic QoL measures have also been used in some trials, such as the EQ–5D or SF–36. Objective outcome measures include blood IgE levels.

Treatment

The British Society for Allergy and Clinical Immunology (BSACI) have produced guidelines[4] for the management of allergic rhinitis. Management may include allergen avoidance, medication (pharmacological treatment), education and immunotherapy.

BSACI guidelines can be summarised as follows. Following diagnosis, first-line treatment of allergic rhinitis is allergen avoidance (where possible and practicable). The nature and severity of symptoms determines the type of medication offered. If symptoms are mild a non-sedating oral or topical H1-antihistamine is given. Where symptoms are moderate to severe, first-line therapy is with a topical intranasal steroid. If these treatments fail further agents may be added according to the troublesome symptom – ipratropium for watery rhinorrhoea, a non-sedating H1-antihistamine for itch or sneeze, a leukotriene-receptor antagonist for catarrh if asthmatic. Blockage of the nose may require a decongestant, oral corticosteroids or a long-acting non-sedating H1 antihistamine. If there is further treatment failure, and if the symptoms are predominantly due to one allergen, then immunotherapy may be considered. The guidelines lack specific or broadly authorised recommendations for immunotherapy, which may be a reflection of the lack of an international consensus to date on the role of this therapy.[12] There are currently no NICE guidelines on treatment of allergic rhinitis.

A survey[13] of UK general practices found that 54% of patients with seasonal allergic rhinitis reported partial or poor control of their symptoms. Of these, 69.4% were not taking their medication as per current

guidelines, the remaining 30.6% were already using their drugs as per guidelines and were still sub-optimally controlled. For these patients immunotherapy may be beneficial.

Immunotherapy

Allergen immunotherapy is a method of reducing sensitivity to a specific allergen by repeated administration of a dose of that allergen. The benefit is dependent on the dose and the route of administration. Various mechanisms have been proposed to explain the efficacy of immunotherapy, including the induction of allergen-specific IgG4, deviation of allergen-induced cytokine production, and allergen-specific T regulatory cells that reduce the late-phase response to the allergen. For any form of specific immunotherapy, the patient's symptoms must be attributable to one or a few dominant allergens.[12]

There are different routes of administration for specific allergen immunotherapy: subcutaneous (injection), sublingual, nasal and oral. For subcutaneous (injection) immunotherapy, weekly injections of incremental doses of allergen are given until a maintenance dose is reached. This maintenance dose is given monthly for 2–3 years. Injections can cause minor adverse events and, whilst systemic reactions are rare, occasional fatalities due to anaphylaxis have been reported.[14] Nasal administration is thought to be effective, but may be limited by local side effects, whilst studies assessing the oral route have indicated a lack of efficacy. Trials comparing sublingual immunotherapy to placebo have found significant reductions in symptoms and medication requirements.[14]

Immunotherapy can be effective in the treatment of symptoms of allergic rhinitis and is the only treatment that can have an effect upon the natural history of the condition i.e. offer long term remission.[4] In one randomised controlled trial a three- year course of immunotherapy to grass pollen remained effective three years after treatment ceased.[15] Where patients have allergic rhinitis only, immunotherapy may prevent the onset of asthma, as shown by the results of a10-year multicentre prospective study of immunotherapy in children with seasonal allergic rhinitis.[16]

There are two licensed products available in the UK for the treatment of seasonal allergic hay fever due to grass or tree pollen in patients who have failed to respond to anti-allergy drugs. Pollinex® (grasses and rye or tree pollen extract) is given by subcutaneous injection, but this was licensed in the 1970s and uses a shortened dosing regime. Grazax® (grass pollen Phleum pratense extract) was recently licensed and is given sublingually.[17] Furthermore, there is considerable specialist use of unlicensed subcutaneous immunotherapy products (mainly Alutard® and Allergopharma®), under CTA (clinical trial authorisation). These include various allergens such as grass and tree pollens, house dust mite, cat and dog danders (personal communication AH). Most recent data regarding the efficacy of subcutaneous immunotherapy is derived from dosage regimes using such products.

Existing research

Clinical effectiveness reviews

The Cochrane review by Calderon *et al.* (2007)[18] identified 51 RCTs comparing subcutaneous (injection) allergen-specific immunotherapy to placebo in patients with seasonal allergic rhinitis. Eight RCTs included participants younger than 18 years and one had an age range of 6–56 years. There were no studies exclusively in children. It is unclear to what extent conventional treatment was inadequate in the included populations. The review found significant reductions in symptom scores and medication use and a relatively low risk of severe adverse events. Searches for this review were completed in February 2006.

The Cochrane review by Wilson *et al.* (2003)[19] included 22 RCTs comparing sublingual immunotherapy (SLIT) to placebo in patients with seasonal allergic rhinitis. The authors found that SLIT significantly reduces symptoms and medication requirements in adults. The treatment effect in children, based on five studies ($n = 218$), was not significant. The treatment appeared to be very safe with no systemic side effects identified in any of the studies. Searches for this review were completed in February 2003. The

review was updated in 2006 and results presented in 2007 at EAACI (European Academy of Allergy & Clinical Immunology) and in 2008 at AAAAI[20] (American Academy of Allergy, Asthma & Immunology) and a further update is due shortly with searches up to September 2009 (personal communication DW). The results of the updated review were broadly consistent with the previous review and showed that sublingual immunotherapy was effective in reducing symptoms and use of medication, with mostly mild side effects.

There is a Cochrane protocol only (McDonald *et al*., 2009)[21] for local nasal immunotherapy for allergic rhinitis.

The systematic review by Penagos (2006)[22] included ten studies of sublingual immunotherapy for allergic rhinitis in children and found evidence of effectiveness of immunotherapy compared to placebo. This was confirmed by the review by Larenas-Linnemann (2009), which included later studies. The review by Röder (2008)[23] included 28 studies on the effectiveness of immunotherapy compared to placebo or another route of administration. In contrast to the reviews by Penagos (2006) and Larenas-Linnemann (2009), the authors found no evidence of benefit for sublingual immunotherapy. Moderate evidence of effect was found for nasal immunotherapy. (It should be noted that these reviews included some trials where the children had house mite allergies).

Head-to-head comparisons of different routes of administration of immunotherapy

Compared to the evidence base of immunotherapy compared to placebo, there appear to be few studies directly comparing different routes of administration. Two RCTs[24,25] were identified comparing subcutaneous with sublingual immunotherapy. No significant differences were found between the treatments in these two small studies.

Cost-effectiveness reviews

There are several studies, which have conducted cost comparisons only. Ariano (2006)[26] found overall lower costs for subcutaneous immunotherapy compared to symptomatic drug treatment (based on a study with 30 patients with pollen-induced rhinitis and asthma). Pokladnikova (2008)[27] compared the mean costs of subcutaneous with sublingual grass pollen immunotherapy and found that sublingual therapy was cheaper overall. Berto (2005)[28] found that in a study of children with pollen and dust mite induced asthma and rhinitis, sublingual immunotherapy was comparable in cost to conventional treatment. None of these studies incorporate quality of life measurements.

Our scoping search identified four studies that conducted cost-effectiveness analyses and calculated cost per QALY gained. Two of these were based on a large multi-centre RCT[10,11] comparing Grazax® with standard care. Quality of life was measured by the EQ–5D. Canonica (2007) looked at a group of southern European countries (France, Italy, Austria and Spain) and found a cost per QALY of between 13,870 and 21,659 Euros for Grazax® compared to standard care. Bachert (2007)[29] conducted the analysis for a group of northern European countries including the UK and calculated a cost per QALY of Grazax® versus standard care of between 12,930 and 18,263 Euros. These values are all below a threshold of £20,000. Both these studies assumed that, after three years of treatment, tolerance to grass pollen would continue for another six years. A further study (Nasser 2008)[8], also based on the same trial, found a cost per QALY of between £4319 and £11,769 in UK patients with allergic rhinitis co-existing with asthma. The cost was found to be sensitive to duration of effect and productivity at work.

One German study was identified (Brüggenjürgen 2008),[30] which found a cost per QALY of 8308 Euros for subcutaneous immunotherapy compared to symptomatic treatment in patients with allergic rhinitis and allergic asthma. This study was not conducted as part of an effectiveness study, but comprised a model with inputs estimated from various literature sources or informed by an expert panel. The cost per QALY was found to be sensitive to costs of subcutaneous therapy and the target population (e.g. age).

We did not identify any cost-effectiveness studies solely in children.

Rationale for project

Allergic rhinitis is an increasing problem with high associated costs, both monetary and social. Conventional therapies cannot control symptoms well for all patients and do not represent a cure. There is a wealth of evidence in the form of randomised controlled trials, particularly for adults, which overall shows benefit of immunotherapy over placebo. Despite this, there is a lack of clear guidelines in the UK on whether immunotherapy should be recommended as standard where conventional treatments have failed. There are two well conducted Cochrane reviews, with the one on sublingual immunotherapy due to be updated shortly (searches up to September 2009, personal communication DW). The searches for the one on subcutaneous immunotherapy were completed in 2006, and we would expect to identify additional data for the time period 2006–2010 as this is a topic of ongoing interest. Further data from the final years of the GT08 Grazax® trial are also expected by the time this project would commence (personal communication AH).

For children there is a smaller evidence base, with some reports finding conflicting evidence of effectiveness for immunotherapy. A definitive and up-to-date conclusion on the evidence of effectiveness for children for both sublingual and subcutaneous immunotherapy is clearly needed.

None of the above reviews include an economic evaluation. A scoping search identified four studies that generated cost-effectiveness estimates in terms of cost per QALY gained, for sublingual (three studies) and subcutaneous immunotherapy (one study). However, none of the cost-effectiveness analyses were based on a systematic review of clinical effectiveness. The two main cost-effectiveness analyses (Canonica 2007 and Bachert 2007) made an assumption of ongoing tolerance to grass pollen for six years after treatment. The availability of further data from the GT08 Grazax® trial would provide further evidence on long-term effectiveness and make an economic model less reliant on assumptions. We did not identify a cost-effectiveness analysis/model solely for children, or for a comparison of different routes of administration of immunotherapy.

For these reasons we believe that a cost-effectiveness analysis/economic model for both adults and children based on an up-to date systematic review of clinical effectiveness is necessary and could contribute to establishing more specific UK guidelines on whether immunotherapy should be recommended, and for whom.

Research methods

Key research questions

Based on the scoping search and clinical advice, we have found little evidence that oral or nasal immunotherapy is of benefit or likely to be used in practice, and we will therefore not include these types of immunotherapy. The key questions are thus as follows:

Clinical effectiveness

1. To identify the evidence for the clinical effectiveness of sublingual specific allergen immunotherapy compared to standard care in adults and children.
2. To identify the evidence for the clinical effectiveness of subcutaneous specific allergen immunotherapy compared to standard care in adults and children.
3. To identify the evidence for the relative clinical effectiveness of sublingual versus subcutaneous allergen immunotherapy in adults and children.

Further questions of interest are:

- duration of effect/recurrence of symptoms
- adverse events
- evidence for the prevention of asthma or other allergies
- most effective dose and dosing regimen

- impact of findings on policy.

Cost-effectiveness

Cost-effectiveness modelling will be performed based on the systematic review evidence of clinical effectiveness. Preliminary research questions are:

1. To determine the cost-effectiveness of sublingual immunotherapy compared to standard care in adults and children.
2. To determine the cost-effectiveness of subcutaneous immunotherapy compared to standard care in adults and children.
3. To compare the cost-effectiveness of subcutaneous versus sublingual immunotherapy compared to standard care in adults and children.

Future research

Any gaps in the current evidence base will be highlighted and will inform recommendations for future primary research. This will include recommendations on study design, populations, intervention, comparators and relevant outcomes based on the EPICOT guidelines.[31]

Search strategy

A scoping search has already been undertaken, which involved interrogation of bibliographic databases such as MEDLINE and EMBASE, health economic databases, the Cochrane Library and HTA websites. The purpose of this was to identify existing reviews and cost-effectiveness studies, to inform this project description, and to gauge the number of relevant studies likely to be included.

Given that there are two relevant well-conducted Cochrane reviews on sublingual and subcutaneous immunotherapy (reviewing 73 RCTs), we plan to build on these and update the searches rather than repeat them. New searches will thus run from 2006 to 2010. Separate searches will be performed to identify relevant studies on cost-effectiveness and for relevant economic model parameters. Search strategies will be developed by an experienced information specialist. Search filters for study design will be included where possible. A combination of text words and index terms relating to the condition and the treatment will be used. There will be no language restrictions.

The following sources will be searched:

- bibliographic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Science Citation Index)
- MEDLINE, EMBASE, NHS EED for studies relating to cost and cost-effectiveness
- Current Controlled Trials *meta*Register, ISRCTN database and ClinicalTrials.gov for ongoing studies
- consultation with experts in the field
- checking of reference lists of relevant reviews
- selected websites
- hand-searching of a selection of relevant journals guided by clinical expertise in the project team.

Study selection strategy

Titles and abstracts of retrieved studies will be screened independently for inclusion by two reviewers. Where it is unclear whether studies meet the inclusion criteria on the basis of title and abstract, full copies will be obtained for assessment. Any discrepancy between reviewers will be resolved through discussion or referral to a third reviewer. The following inclusion and exclusion criteria will apply to clinical effectiveness studies:

Study design

Randomised controlled trials (RCTs). RCTs constitute the most robust form of evidence and given the availability of in excess of 73 RCTs, we are unlikely to extend the inclusion criteria to other study designs.

However, if we find that there is insufficient long-term follow-up data for use in the economic model, we may look at large well-designed cohort studies. Scoping searches indicate that follow-up times of RCTs vary between less than six months to more than a year.

Population

Adults or children with a confirmed diagnosis of seasonal allergic rhinitis (hay fever). Confirmation is likely to be through a skin prick test and/or blood test. If we identify any trials where patients have been included on the basis of symptoms only, we will include these and consider them separately. Patients with co-morbidities such as asthma will be included.

The brief specifies adults and children (examined separately) with severe hay fever, which does not respond to conventional treatment. We anticipate that not all trials will provide this information, or use different classifications for 'severe' or 'not responding to conventional treatment'. Where the information is provided, populations may still be heterogeneous. Where possible we will consider trials (or subgroups of trials) separately where patients meet specified severity criteria.

Where we are using existing Cochrane reviews, we will check whether the included trials meet our inclusion criteria.

Intervention

Allergen-specific subcutaneous (injection) or sublingual immunotherapy in any setting. There will be no restrictions regarding a particular dose or dosing regimen.

Comparator

This is likely to be placebo in most cases, with conventional (rescue) medication given alongside in both treatment arms. We will also include as a comparator a different route of administration of immunotherapy.

Outcomes

As specified in the brief, at least one of the following will need to be reported for the trial to be included: symptom severity, reduction in medication, cost-effectiveness, frequency of exacerbations, quality of life, adverse events, dose-effect relationships. We are also interested in any studies reporting the prevention of new asthma cases.

Data extraction

Data extraction will be performed by one reviewer and independently checked by a second reviewer. A piloted data-extraction form will be used. Data will be extracted on trial design, patient characteristics, intervention (route of administration, dose, frequency), comparator and outcomes.

Quality assessment

Quality assessment of all included studies will be performed using the Cochrane guidelines[32] on assessment of risk of bias (selection bias, performance bias, attrition bias, detection bias, reporting bias). Of particular importance to these trials is blinding of patients, investigators and outcome assessors, due to the subjective nature of some of the outcomes (e.g. reduction in symptom severity).

Data synthesis

As there is a large number of trials, meta-analysis has been undertaken in the two relevant Cochrane reviews. We would expect to update these analyses using Stata 10 where new data is available. If data is available, we will also consider conducting meta-analysis for immunotherapy in children.

There is likely to be a large amount of heterogeneity between trials, for example in terms of how patients were recruited, severity of hay fever, type of allergen, dosage as well as route of administration. We will examine clinical and statistical heterogeneity before attempting to pool data. There are also likely to be a

variety of outcome measures used to measure reduction in symptom severity, therefore the standardised mean difference will be used when pooling data. Studies on sublingual and subcutaneous immunotherapy will be pooled separately. Where we are unable to incorporate study results into meta-analyses, these will be tabulated and described separately, and the consistency of the results with those of the meta-analyses discussed.

The likelihood of publication bias will be investigated through the construction and evaluation of Funnel plots.

We are likely to identify only few head-to-head trials of different routes of administration. We will investigate the possibility of conducting an indirect comparison, however this is likely to be hampered by heterogeneity between the studies.

Economic evaluation

Literature review

A formal search will be undertaken as outlined in section 3.2 in order to identify additional studies reporting cost or resource use, quality of life and cost-effectiveness. Relevant cost-effectiveness studies will be summarised formally appraised using the Drummond checklist[33] and may be used to inform the model. Information on the following key items will be extracted: type of economic analysis, population, intervention, comparator, perspective, time horizon, structure and assumptions of model, effectiveness data, resource and cost data, discounting and results of base case and sensitivity analyses.

We will conduct a systematic search of the QoL literature in order to identify studies that directly measure utility values for example through the use of the EQ–5D.

Economic model

Depending on the suitability of existing models we may adapt these, or develop our own model. The model structure will be informed by the patient pathway and will be developed with the help of our clinical experts. As this is a long-term disease we are likely to use a state transition model such as a Markov model.

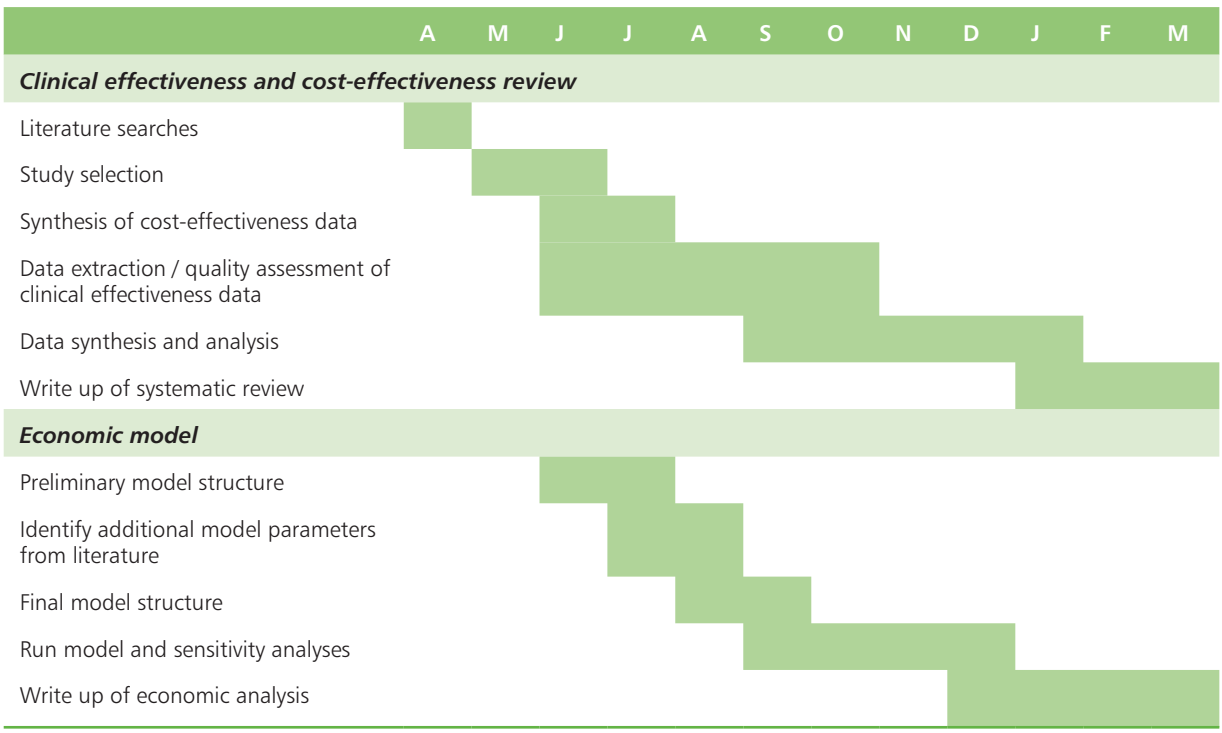
The systematic review of effectiveness will generate the most evidence based parameters to be used in the economic model. Depending on the extent of the evidence base, these may not be summary estimates but represent qualified, best estimates representing current practice. Trials that have measured QoL using the EQ–5D such as the large multi-centre trial[10,11] of Grazax® will be particularly useful. We will approach the trial investigators in order to obtain, if available, effectiveness and QoL data beyond three years (on which the previous economic evaluations were based). Where studies have measured QoL using outcome measures other than the EQ–5D, we will investigate whether QoL results can be converted into a form that will allow them to be combined with the EQ–5D values. Drug and resource costs will be obtained from the literature review, standard sources, and consultation with clinical experts. These will include costs of medication, GP visits, hospitalisation and hours lost from work. We will also include the costs resulting from adverse events wherever possible.

The results of the economic modelling will be expressed as incremental cost per QALY gained. We will run the model using a 'base case' scenario, which will be varied for a number of sensitivity analyses. Parameters which are expected to influence the cost per QALY are drug costs, duration of benefit and population characteristics. If the available data allows, we will conduct separate analyses for adults and children and for subcutaneous and sublingual immunotherapy. Deterministic and probabilistic sensitivity analyses will be undertaken. Decision uncertainty will be displayed through the use of cost-effectiveness acceptability curves and value of information analysis as appropriate. If the evidence is available we will also look at different types of allergen (e.g. grass, tree). We will attempt to incorporate costs savings of prevented cases of asthma.

Our scoping searches indicate that the most evidence is likely to exist for sublingual immunotherapy with grass pollen versus conventional treatment and this is likely to be the primary focus of the economic model. We will however endeavour to also model subcutaneous immunotherapy versus conventional treatment, as well as a comparison between sublingual and subcutaneous administration.

Project timetable

The project is expected to run over a 12-month period. Key stages are outlined below:



Milestones

At 3 months: all relevant studies for inclusion into systematic review identified; preliminary model structure.

At 6 months: submission of HTA progress report; final model structure.

At 7 months: all data extracted and quality appraised.

At 10 months: all data synthesis/analysis completed, all model sensitivity analyses completed.

Expertise

The applicants have extensive experience of conducting systematic reviews and health technology assessments, meta-analysis, economic modelling, information science and clinical immunology. The West Midlands Health Technology Assessment Collaboration (WMHTAC) members have worked together successfully on numerous previous projects and have no commercial interests in their projects.

Janine Dretzke (JD) has been a systematic reviewer with WMHTAC since 2001 and was the main reviewer on four large HTA reports (for NICE/NETSCC HTA), working closely with health economists, clinical experts and information specialists. JD has considerable experience in the subject of this proposal as she has recently completed a systematic review of clinical and cost-effectiveness on provocation/neutralisation testing in food allergy and also contributed to a review on acupuncture for allergic rhinitis. JD will contribute mainly to the systematic review of effectiveness, data analysis and report writing.

Dr Catherine Meads (CM) is a senior systematic reviewer and the Director of WMHTAC. This collaboration has conducted numerous HTAs, systematic reviews and other evidence synthesis reports for a variety of customers including the NIHR HTA programme over the last ten years. She has experience of managing large research grants, particularly for National Institute for Health and Care Excellence (NICE) Technology Appraisals and for the Centre for Public Health Excellence. CM has worked in the Unit of Public Health, Epidemiology and Biostatistics for over 12 years and has extensive systematic review experience, having worked on numerous systematic reviews for NICE, NIHR and other customers. CM will contribute to the systematic review of effectiveness, management of the project and report writing.

Professor Jayne Parry (JP) is the Head of the Unit of Public Health in the University of Birmingham and has an active research programme focusing on the evaluation of health impacts of public policy. She is a senior researcher with excellent project management skills and substantial experience of leading multi-disciplinary research teams. JP will provide input into project management and any other duties as required.

Dr Pelham Barton (PB) is a highly experienced mathematical modeller whose main research area is the application of appropriate simulation modelling techniques to choose between a range of possible strategies for treating a given patient group. He has many published models, dealing with both hospital-based health care interventions, where the focus is on individual patient pathways, and health care interventions where it is essential to consider the effects on the whole population. PB joined the Health Economics Unit in the School of Health and Population Sciences in 1998 and has been closely involved in the WMHTAC technology appraisals for NICE. PB will supervise a health economist, who will carry out most of the work on the economic component, and will contribute to the economic modelling and report writing.

Dr Kristina Routh (KR) is a medical doctor in her final year of Higher Specialist Training in Public Health. Previously trained in Pathology, she has over five years experience of working within a variety of health organisations at both local and regional level. Her public health training will allow her to bring a population-based perspective to this review and, having worked both within the Regional Specialised Commissioning Team and with commissioners in two Primary Care Trusts, she will contribute valuable insights into the requirements of commissioners. KR will contribute to data analysis and report writing, particularly with regard to policy impact.

Anne Fry-Smith (AFS) is a senior information specialist, who leads the information team supporting WMHTAC and ARIF. She has extensive knowledge of research information searching and retrieval strategies. She is the co-author on several NICE reports. AFS will develop and run the search strategies.

The following clinical experts (AH, TK, DW) will support the team with clinical input and access to contacts. Further, we anticipate forming a steering committee consisting of the clinical experts as well as PB, CM and JD in order to ensure that the economic component of the review links up with the clinical effectiveness component, and to enable clinical input to inform the structure of the model from the outset.

Dr Aarn Huissoon (AH) is a consultant immunologist at Birmingham Heartlands Hospital (Heart of England NHS Foundation Trust) and honorary senior lecturer at the Department of Immunity and Infection, University of Birmingham. He has been providing an allergy service including desensitisation immunotherapy for allergic rhinitis for the last 8 years. AH is the local investigator for a number of multicentre placebo-controlled trials of both subcutaneous and sublingual immunotherapy for allergic rhinitis and can therefore bring first-hand in-depth experience of both clinical use and investigation of immunotherapy to the team. In addition he has undertaken a course in systematic reviews, and has published a review of acupuncture in allergic rhinitis.

Dr M Thirumala Krishna (TK) is a consultant immunologist and allergist and honorary senior lecturer at Birmingham Heartlands Hospital. His main interests include allergen immunotherapy and novel treatments in allergic disease, and air pollution and health.

Dr Duncan Wilson (DW) is a consultant respiratory physician at Selly Oak Hospital (University Hospitals Birmingham). His main clinical interest is in airway allergy: allergic rhinitis, asthma and the link between those two conditions. His MD thesis covered clinical and immunological aspects of specific allergen immunotherapy. As well as his clinical duties, he is an honorary senior lecturer at the University of Birmingham and is Clinical Service Lead for Respiratory Medicine. He is the main author of one of the relevant Cochrane reviews on sublingual immunotherapy for allergic rhinitis, and is also involved in the upcoming update of this review. DW can thus act both as a clinical advisor and give advice on systematic review methodological issues.

Service users

Patients who suffer from severe hay fever will have views on the usefulness and appropriateness of immunotherapy treatment. AH has extensive patient contact and is well placed to approach a patient or patients who would act as a patient representative(s) on the project. A patient perspective will help us to put the findings of our review into a patient-relevant context. We also propose to disseminate our findings to service users through leading charities such as Allergy UK (www.allergyuk.org), for example by contributing to one of their Allergy Fact Sheets.

Justification for the support requested

We have, as a group of applicants, very carefully analysed the degree and complexity of the work required to produce high quality clinical effectiveness reviews and economic model. We are in an excellent position to gauge the level of resources required to deliver this type of project as we have several years experience in the delivery of such projects in a variety of topic areas.

We think that one year will be a sufficient time scale for all the work proposed in this application. We have recently conducted similar projects involving systematic reviews and economic modelling for a several customers and the nature of this project is similar in complexity and workload to previous projects. We have found that a senior reviewer with a medical background is invaluable because of the complex nature of the clinical terminology and lack of reporting standards in clinical and methodological terms. The burden of work related to effectiveness review will require two reviewers to enable double study selection, data extraction etc. but neither need to be full-time. For the modelling work, one modeller will need to focus on this work full time for six months, with supervision from the experienced senior modeller. Funding is therefore requested for:

- One systematic reviewer 0.2 WTE and one systematic reviewer 0.5 WTE for 1 year who will carry out mainly the effectiveness review.
- One WTE health economist for 6 months for the economic evaluation.
- Suitable supervision for the clinical effectiveness, economic modelling and the project as a whole.
- A small amount of time from an information specialist, appropriate for one project.

As this work will be performed by staff embedded within a larger HTA organisation, we are able to draw on additional in-house expertise as necessary. In addition, some WMHTAC team members are core-funded so not being paid to work on this project.

The non-staff costs comprise the following:

- Travel and subsistence for one conference to disseminate findings of the research.
- The consumables budget of £1,000 is based on our experience of the number of inter-library loans required for a systematic review, and sundry other administration costs. The small amount for consultancy will be used to nominally reimburse our clinical experts for their time, particularly Dr Aarn Huissoon who will be closely involved with the project

References for original protocol

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